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A.M.A. ARCHIVES OF

INTERNAL MEDICINE

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Cecil J. Watson

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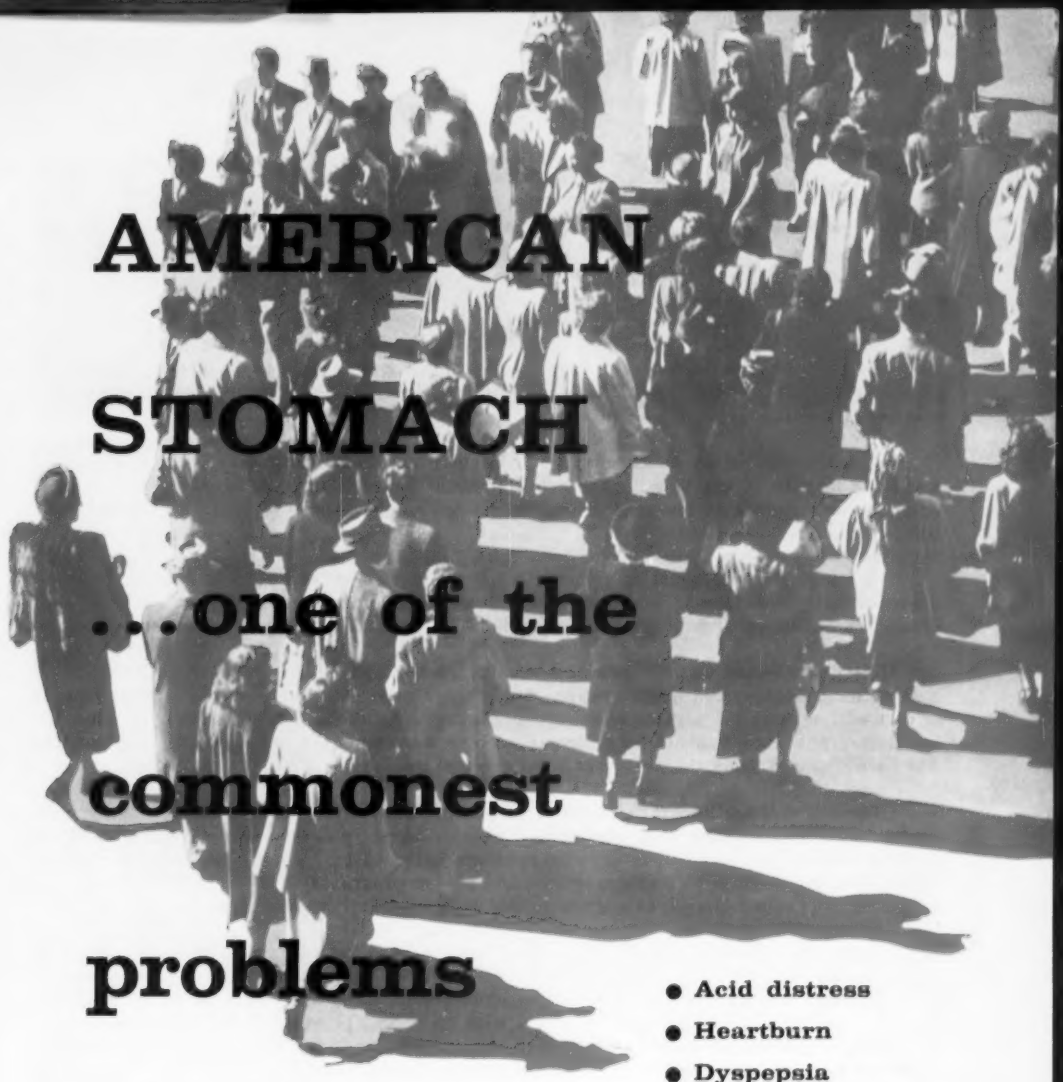

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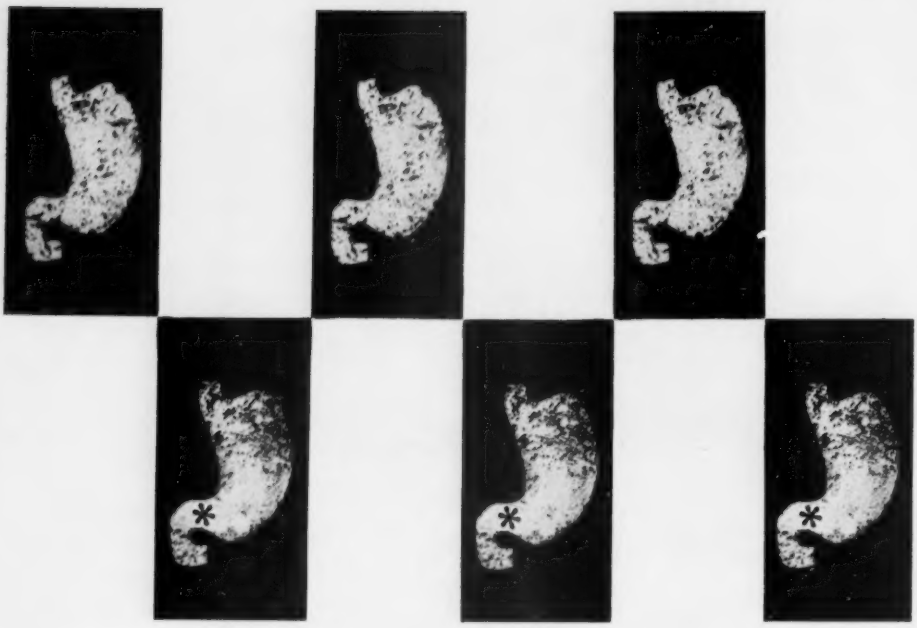

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Porphyrin Metabolism in the Anemias

The George Richards Minot Lecture

CECIL J. WATSON, M.D., Minneapolis

I count it a special privilege and honor to have been invited to give the sixth George Richards Minot Lecture of this section. I have a strong personal feeling about this because over a period of quite a number of years George Minot stimulated and aided my research and was most generous with his advice and friendship on many occasions. Among many fine and interesting qualities, one of the most appealing that he had, in my opinion, was that of helping and encouraging young men along the tortuous path of medical research. He is famous for his notes to young investigators, often penny post cards in his own handwriting, telling them of his interest in one of their recent papers. He was considerate in his praise, just and meticulous in his criticism. His use of the English language was never dull, and it was often quaint and amusing. In the first of this series of George Minot lectures, one that I can strongly recommend to any who have not read it, Dr. William Castle [1] relates a classic pearl which Dr. Minot produced in a speech in Boston in 1929. "One must always be prepared to recognize that but a hair above the underbrush may mean a large mammal is at hand."

Dr. Minot was keenly interested in the subject on which I wish to speak in this lecture. Indeed, he provided much help and encouragement to my earlier studies in this area. He was specially interested in the problem of the porphyrins in relation to erythropoiesis, and in 1939 he volunteered to obtain financial assistance to permit me to purchase a microfluorospectrometer. This was to have been assembled by optical companies in Munich and Vienna, but unfortunately the curtain of World War II came down before the purchase could be consummated. Nevertheless, it has been possible in subsequent years to assemble such an apparatus, and I wish to consider it briefly in connection with some of our findings.

The possession of a microfluorospectrometer, which has been in process of construction in our laboratory since 1948, has permitted a study of the content of porphyrin in the developing red blood cells of the bone marrow. While it is believed that eventually the apparatus will permit a differential semiquantitative determination of porphyrins in individual cells, it has been of principal value thus far in detecting and localizing porphyrin by virtue of its red fluorescence and gaining a rough idea of its relative amount. It has been of aid to plot fluorescing cells in a given field of an unstained preparation, then, after staining with Wright's

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or another suitable stain, to study the same cells morphologically, also any other cells now in evidence but which were not seen in the unstained preparation because they did not fluoresce. This information, coupled with fractional quantitative determinations by suitable micromethods, has provided insight as to the location and type of porphyrin in bone marrow and other cells. With this combined technique some decisive results were obtained in a study with Schmid and Schwartz of the rare but key disease which we have designated "erythropoietic" porphyria, in contrast to the hepatic forms of the disease.[2] The erythropoietic type is often, perhaps always, associated sooner or later with a hemolytic anemia, but the primary disturbance is an excessive elaboration of porphyrins of isomer Type I, which is normally formed in but very small proportion with the Type III porphyrins of the various heme proteins. Studies with the fluorescence microscope in cases of erythropoietic porphyria[2] revealed that porphyrin concentration was much greater in the nuclei of the developing normoblasts in the bone marrow. The cytoplasm contains smaller amounts which may well have emanated from the nuclei. It is evident that certain of the normoblasts, indistinguishable by ordinary staining methods, do not participate in the excessive porphyrin formation. There is reason to believe that the Type I uroporphyrins and coproporphyrins are in part actually secreted by these cells, to account for the great excesses in the urine.[2] A part however, is probably derived from the destruction of porphyrin-laden erythrocytes in the spleen, as the splenic porphyrin concentration is high. The excessive porphyrin formation in the abnormal nucleated red blood cells may be regarded as the essential metabolic error of this form of porphyria. That it occurs in the nuclei may well be related to the fact[3] that the important porphyrin precursor, δ-aminolevulinic acid, is also utilized at least to some extent in the formation of purines.

The combined fluoromicroscopic and analytic technique thus permitted a clear delineation of erythropoietic porphyria, a true blood dyscrasia, from the much commoner hepatic types in which there is no evidence of porphyrin disturbance in the bone marrow but rather a disturbance of porphyrin metabolism in the liver.[2]

In erythropoietic porphyria the circulating red cells contain large amounts of uro- and coproporphyrin I, but the amount of protoporphyrin is normal or not more than slightly increased, and it is probable that this is mainly Type III isomer, which is normally present and markedly increased under a variety of circumstances, as will be mentioned in the following. It has long been known that lead intoxication causes striking increases of protoporphyrin 9 (Type III) in the circulating red cells and of the corresponding coproporphyrin III in the urine. Schwartz, Keprios, and Schmid[4] found that a type of erythropoietic porphyria could be produced experimentally by the combination of lead poisoning and a strong stimulus to erythropoiesis as provided by phenylhydrazine hemolysis. In acute lead poisoning alone there is already a great increase of uro-, copro-, and protopophyrin in the bone marrow,[5] while in the circulating red cells the excess is mainly protoporphyrin, with varying increases of coproporphyrin. With less acute poisoning smaller amounts of uroporphyrin are observed in the bone marrow, and the erythrocyte coproporphyrin (ECP) is much less prominent, while with chronic poisoning the bone marrow characteristically exhibits only excesses of copro- and protoporphyrin and the circulating red cells only protoporphyrin. If phenylhydrazine hemolysis is added to the disturbing effect of acute lead poisoning on hemoglobin metabolism, the excessive porphyrin formation in the bone marrow and excretion in the urine is much more outspoken, and under these circumstances a veritable erythropoietic porphyria is produced. It differs, however, from the human congenital type in that while the uroporphyrin formed is

mainly Type I, the copro- and protoporphyrins are mainly Type III.* This apparent discrepancy and the curious contrast which it makes with the human form at once raises important questions about the whole problem of porphyrin biosynthesis, in relation to hemoglobin formation. It is desirable to consider this matter briefly before going on to other disturbances of porphyrin metabolism in the anemias.

Recent studies by Shemin and co-workers,[3,6-8] Cookson and Rimington,[9,10] Neuberger[11] and their associates have clearly delineated the primary steps in the biosynthetic pathway, as involving the formation of δ-aminolevulinic acid from glycine and a succinyl derivative, condensation of two molecules of this acid then providing the monopyrrol, porphobilinogen. This substance is not in evidence under normal circumstances, and indeed its appearance is largely limited in human disease to the liver and urine in cases of acute porphyria. Nevertheless it is often present in small amount in the urine in cases of lead poisoning,[12,13] and in the above-mentioned experimental lead-phenylhydrazine porphyria it occurs in the urine in much larger amounts.[4] In these latter situations its appearance is quite likely related to a disturbed hemoglobin formation, while in human acute porphyria it is believed to be formed in the liver as a result of disturbed synthesis of heme enzymes other than hemoglobin.[2] Porphobilinogen is a monopyrrol with propionic and acetic acid sidegroups. Four molecules readily unite to form uroporphyrin, a tetrapropionic tetra-acetic acid substituted porphyrin. Various studies[14-17] have now demonstrated that tissue systems such as red cell hemolysate or liver homogenate readily convert porphobilinogen to uro-, copro-, and protoporphyrin. Until recently, however, it was not certain whether these were formed by successive decarboxylation from uro- to copro- to proto-, and indeed the majority of studies had failed to indicate that such a conversion occurred. Grinstein, in an earlier publication,[19] had suggested that coproporphyrin was the immediate precursor of protoporphyrin, and I[20] had favored this view on the basis of various indirect evidence, some of which will be referred to a little later. Salomon and coworkers[21] believed to have demonstrated conversion of uroporphyrin to heme in rabbit bone marrow, in vitro. Eriksen[18] described evidence suggesting such a pathway, but extensive studies by Schwartz,[16] in this laboratory, and also by Dresel[15] and Shemin[22] failed to support a direct interconversion from uro- to copro- or copro- to protoporphyrin. It has recently become clear, though, that an interconversion readily proceeds if the porphyrin is in the reduced state. Thus Neve and Aldrich[23] have demonstrated increased uptake of Fe^{59} after addition of reduced uroporphyrin to red cell hemolysate. In our own laboratory, studies with Bashour[24] and Schwartz, using N^{15}-tagged reduced uroporphyrin I and C^{14} uroporphyrin III, in individual studies, have revealed conversion to the corresponding coproporphyrin either in dog liver homogenate or chicken red cell hemolysate. Conversion of labelled coproporphyrinogen III to protoporphyrin was also observed. Suggestive evidence of the formation of a Type I protoporphyrin from coproporphyrinogen I was obtained, but this was not proven. These observations strongly support the view that the pathway in vivo is from porphobilinogen to a reduced uroporphyrin ("prouroporphyrin" or "uroporphyrinogen"), thence to a "procoproporphyrin," and finally to protoporphyrin and heme (Fig. 1). The possibility that the in vivo mechanism depends upon partial decarboxylation of some fraction of the porphobilinogen and independent formation of the three porphyrins cannot be excluded, but the former mechanism is more plausible and fully supported by the recent studies just referred to. It is also

* Phenylhydrazine alone causes a moderate increase in excretion of coproporphyrin I in the urine of rabbits and an increased relative concentration of this porphyrin in the circulating erythrocytes (Ref. 32 and unpublished data of H. M. Wikoff and S. Schwartz).

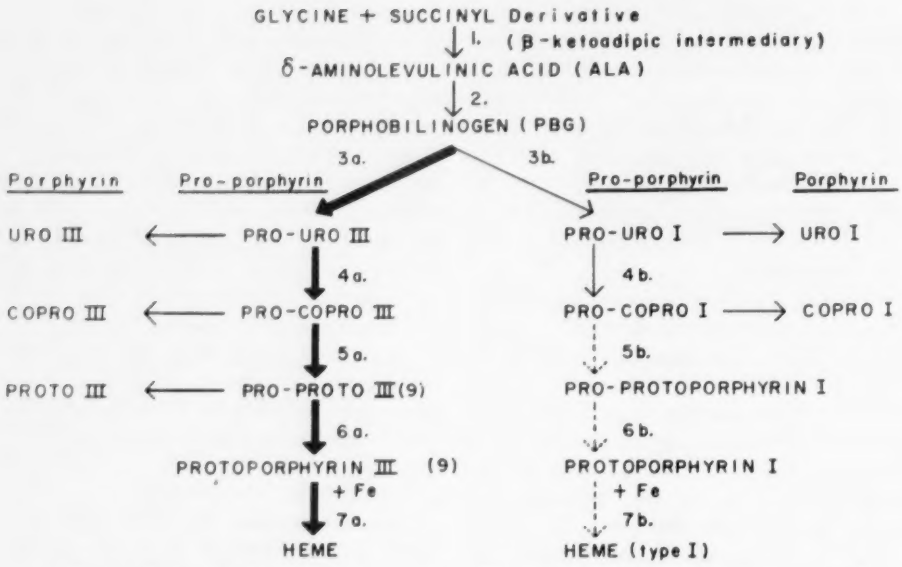

Fig. 1.—Pathways of porphyrin biosynthesis. The existence in nature of pro-, uro-, and procoproporphyrins has been shown [25]; that of a protoporphyrinogen, however, is purely hypothetical and need not be assumed, as it is possible that protoporphyrin is formed directly without an intermediate porphyrinogen. The broken arrows in the b pathway on the right indicate possible transitions for which no evidence is thus far available.

borne out by the natural occurrence of proporphyrins or porphyrinogens which are similar if not identical to those formed by amalgam reduction in vitro.[25]

In passing, it is safe to say that George Minot would have been intensely interested in the recent studies of Sir Alexander Todd and co-workers, revealing that vitamin B_{12} contains a porphyrin-like ring which complexly binds the cobalt of the molecule. Recent studies [46] in collaboration with Merck & Co., Inc., have shown that C^{14} porphobilinogen is readily utilized in the formation of vitamin B_{12} by Streptomyces griseus (Addendum).

The condensation of four molecules of porphobilinogen might give rise to any one or a mixture of the four uroporphyrin isomers.[10] As Rimington [26] suggested a number of years ago, it is quite likely that the direction of biosynthesis is subject to enzymatic control. Under normal conditions this is exerted almost wholly along the Type III pathway. Nevertheless, small amounts of Type I isomer are formed but, at least under normal conditions, are not utilized and hence are excreted. This probable relationship is shown in Figure 1.

The plan in Figure 1 readily accounts for the preponderance of uroporphyrin and coproporphyrin I in the normal urine and feces as shown. Studies with Bashour [47] reveal a normal range of 5-30 γ of uroporphyrin in the urine and up to 50γ per day in the feces, the Type I isomer preponderant in the urine. Data on the fecal uroporphyrin are thus far inadequate and actually relate to the total ether-insoluble porphyrin, very likely including porphyrins with six or seven as well as eight carboxyl groups. This is also true of the urinary uroporphyrin. The normal range of coproporphyrin in the urine is from 60-280 γ [27] per day, of which from 60%-80% is Type I isomer.[28] The range of coproporphyrin in the feces in 43 normal adult humans, mainly men, was found to range from 322-1468 γ per day, mean 613.7 ± 254.9.[48] In 14 of these which were further analyzed the percentage of Type I isomer was found to range from

86%-97%. It will be quite evident from all of these data that the original basis of designation of the uro- and coproporphyrins, i. e., their occurrence in urine or feces, respectively,[29] is only relative. The terms are also somewhat unfortunate in failing to express the important relationship of these porphyrins to the intrinsic anabolic pathway of heme synthesis, as discussed above.

Erythropoietic porphyria may be due to an abnormal, probably enzymatic, stimulus of uro- and coproporphyrin I formation in some of the developing red blood cells of the bone marrow. In lead poisoning, however, the situation is more complex, with excessive uroporphyrin I and especially coproporphyrin III in evidence. If these observations are considered in relation to the plan in Figure 1, various interpretations are possible. Since porphobilinogen is regularly encountered in the urine in small amount, some hindrance in uroporphyrin formation may be postulated, in which uroporphyrin I formation is relatively emphasized, with its appearance in the bone marrow and urine.[4,31] The failure of coproporphyrin I to appear in any considerable amount is difficult to understand, but this suggests an interference at Stage *4b* in Figure 1. At the same time, the appearance of such large amounts of coproporphyrin III as typify the urine in lead poisoning, indicates some type of interference at Stage *5a*. An abnormal, immediate conversion of the porphyrin or porphyrinogen to the coproporphyrin itself would suffice, though some other form of partial block at this point of normal conversion is not excluded. Evidence of further interference is observed at Stage *7a* in that the circulating red cells in lead poisoning contain large excesses of protoporphyrin. This interference may be only relative in character in the sense of an actual overproduction of precursors. The failure to observe uroporphyrin III† in the bone marrow or excreta is unexplained, unless one assumes that lead is remarkably selective in the points at which it exerts its disturbing effect. Despite such interferences, hemoglobin formation is completed in considerable measure. Even with marked anemia, it is evident that the amounts of new heme entering the blood stream in young red cells are considerably greater than the amount of free porphyrin in new erythrocytes or that in the excreta for the same period of time. There is also a possibility of a disturbed porphyrin synthesis in the liver, unrelated to hemoglobin metabolism. While there is no direct evidence for this, it cannot be excluded at the present time.

Up to this point considerable attention has been given to erythropoietic porphyria and lead poisoning, as these are believed to represent key disturbances in porphyrin metabolism. Before going on to discussion of the changes encountered in other anemias the effect of a more normal stimulus on erythropoiesis may be considered in relation to porphrin metabolism. Acute blood loss as well as simple hemolytic activity have been found to be associated with excessive bone marrow and erythrocyte porphyrin concentration.[5,32] Recent studies [5] of bone marrow and circulating erythrocyte porphyrins under such circumstances have revealed that the altered concentrations appear to depend on (1) the extent of increase in rate of erythropoiesis and hemoglobin synthesis (or attempted synthesis, partly unsuccessful, as in lead poisoning), (2) the degree of iron deficiency.

The available evidence indicates that as the rate of synthesis increases there is proportional increase in the amount of ECP (erythrocyte coproporphyrin). With milder stimuli the increase is chiefly apparent in the bone marrow normoblasts, but the protoporphyrin of the circulating red cells (EP) is often moderately increased above the normal range of 20-60 γ/100 cc. of ery-

†It is recognized that significant amounts of this porphyrin may have escaped detection, as the Type I isomer, which predominates, crystallizes much more readily, and smaller amounts of Type III, (or even II or IV) may have been left in the mother liquor.

throcytes.[20] With a greater stimulus to erythropoiesis, the ECP (erythrocyte coproporphyrin) increases significantly above the negligible traces normally present (0-1 γ/100 cc.) and, usually, in rough proportion to the reticulocyte percentage.[20,32] By reference to Figure 1 it may reasonably be assumed that these excesses are due to a rate of formation exceeding the rate of transfer from copro- to proto- and thence to heme (Stages *5a* and *6a*). In the presence of iron deficiency, as induced by blood loss, the amount of EP as well as BMP (bone marrow protoporphyrin) is markedly increased. The EP is often increased into the range characteristic of lead poisoning, in which interference, rather than deficiency, is the responsible factor. In iron deficiency states the exhibition of iron is followed promptly by a progressive decline of the EP to the normal range, yet it is of much interest that edathamil calcium-disodium (Calcium Disodium Versenate), though it quickly abolishes the excessive coproporphyrinuria of lead poisoning,[33] affects the elevated EP much more slowly than does iron in chronic posthemorrhagic anemia.[47] This perhaps suggests that Transfer *5a* in Figure 1, from procopro- to protoporphyrin, may be less sensitive to the effect of lead than Stages *6a* and *7a*. However, the basis of this striking difference in the effect of edathamil calcium-disodium is not yet clear.

The comparison, and in many situations the contrast, of the UCP (urinary coproporphyrin) with EP and ECP is of both fundamental and practical interest, as I shall bring out more fully in a moment. The interest is heightened and the situation at the same time greatly complicated by the varying preponderance of the Type I and III coproporphyrin isomers, more particularly in the urine, in various pathological states. Previous studies of the isomer ratio by the "fluorescence quenching" technique [34] revealed that Type I normally comprises from 60%-80% of the urinary coproporphyrin.[28] This method offers some technical difficulty but is reliable within reasonable limits if carefully used, the results obtained are generally in agreement with those of infrared spectrophotometry,‡ and Chu-Green paper chromatography. It may be noted, however that Comfort and co-workers,[49] using the latter technique, report preponderance of Type III coproporphyrin in normal human urine. The reason for this difference is not clear.

A number of years ago coproporphyrin I was isolated from the feces of pernicious anemia and hemolytic anemia patients.[36-38] The amounts obtained, by comparison with those from normal control samples, appeared to be excessive. Dobriner [39,40] reported significant increases of fecal coproporphyrin I in experimental hemorrhagic anemia and in clinical anemias associated with blood loss or increased blood destruction. The concept was advanced [39,40] that coproporphyrin I excretion was roughly proportional to erythropoietic activity, with a ratio of 10,000 (Type III) to 1 (Type I). More recently, studies by Schwartz and co-workers [41] showed marked increases of coproporphyrin I in feces and urine of dogs with phenylhydrazine anemia. The results of quantitative studies in human anemias, however, have failed to provide evidence of any close correlation between the rate of erythropoiesis and the coproporphyrin I excretion. Data for various cases are given in the Table. By comparison with the normal data mentioned above it is evident that normal values are often observed both in hemolytic anemia and in pernicious anemia in relapse, as well as after blood loss. This apparent lack of agreement with the earlier clinical and experimental data just referred to has not been explained. It is quite possible that actual excesses over the normal range are encountered only when there has been a recent profound stimulus, such as severe acute hemolysis or blood loss. Species differences may be of relative importance. Further study is needed to determine the significance of alterations of values for any given person within the over-all normal range as given

‡ With Dr. Marie Berg and Miss Ruth Cardinal.

Fecal Coproporphyrin Excretion in Certain Anemias

Case	Diagnosis	FCP, γ/Day	Per Cent Type I	Orobilinogen, Mg./Day
1	Pernicious anemia	460	80	410
2	Pernicious anemia	700		95
3	Pernicious anemia	520		
		445		
4	Pernicious anemia	261		
		446	73	
5	Hemolytic anemia with infectious hepatitis	371	89	1,166
6	Idiopathic hemolytic anemia	532	90	1,652
7	Idiopathic hemolytic anemia	153		502
8	Hemolytic anemia	691		354
9	Ch.myel.leukemia	636		151
10	Ch.myel.leukemia	175		39
11	Ch.myel.leukemia (benzene)	709	34	390
12	Hodgkin's disease	375		129
13	Refractory anemia	279	78	68
		158		
		435		
14	Refractory anemia	321		67
		277	45	
15	Refractory anemia	398		135
16	Hypochromic anemia	172	92	72
17	Lead poisoning	800	90	
18	Lead poisoning	760	92	

earlier. The fecal coproporphyrin data in pernicious anemia, relapse versus remission, as published by the author a number of years ago, fall within the normal range, yet the decline with remission appeared significant.

It is also seen in the Table that the values in the hyporegenerative or refractory anemia group, though tending to be low, are not reduced to the extent that might be anticipated if there were a strict relationship between the amount of coproporphyrin I excreted and the rate of erythropoiesis. While these findings do not exclude the traditional concept of copro- I formation represented in Figure 1, they appear to make the idea of a constant ratio with Type III less tenable.

Studies by Schwartz and Wikoff [32] and others [41] revealed that acute hemolytic (phenylhydrazine) anemia in rabbits, with maximal erythropoiesis, is associated with significant increases in the proportion of Type I coproporphyrin in the erythrocytes and urine. It is reasonable to believe that this porphyrin moiety is excreted because unused in heme synthesis and therefore released from the developing red cells, while the Type III porphyrin may well be employed in the formation of additional small amounts of hemoglobin even after the cells have entered the circulation. The available evidence indicates that the content of free porphyrin of the circulating erythrocytes is limited to reticulocytes and fluorescytes, in other words, young cells which have recently left the bone marrow. There is definite evidence that reticulocytes can fabricate new heme, provided the building blocks are available.[42]

In pernicious anemia in relapse, the EP of the circulating red cells is in the normal range and ECP is undetectable, at least with the amounts customarily employed in the determination.[20] The coproporphyrin of the excreta in this disease is preponderantly Type I isomer.[36] It is believed that these findings accord well with the megaloblastic bone marrow, maturation arrest, and reduced effective hemoglobin formation.

The effect of B_{12} is striking; the ECP rises steeply and falls almost as rapidly, the peak lagging very slightly behind that of the reticulocytes, although the curves in general are nearly superimposed.[20] The EP rises more slowly and declines gently over a long period of time.

In the "refractory" or hyporegenerative anemia group quite a different combination of findings is usually obtained. The UCP is often moderately increased, but, more important, the isomer ratio is very often reversed, and in the majority of cases Type III is preponderant (Fig. 2), though the amounts of this porphyrin as a rule are not in the range characterizing heavy metal (Pb, As, Hg) or recent chemical poisoning

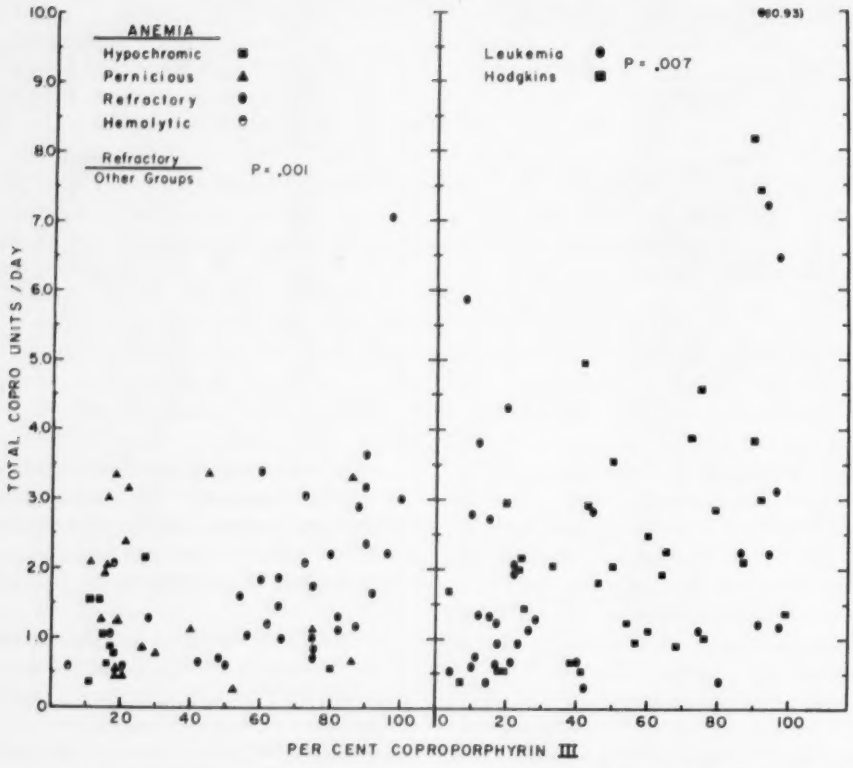

Fig. 2.—Plot of total urinary coproporphyrin and proportion of Type III isomer in various anemias, leukemia, and Hodgkin's disease. On the left the difference in distribution of values for the refractory anemia group as versus the group including pernicious hypochromic and hemolytic anemias is seen to be highly significant (P=0.001); on the right the difference noted between the values for Hodgkin's disease and those for leukemia is also significant, though not to the same degree (P=0.007). The unit scale for total coproporphyrin on the ordinate relates to two different methods used at different periods. With the earlier of these, the upper limit of normal was 100 γ/day,[38] and with the later, 280 γ/day.[37] For the present plot values obtained with the later method have been divided by 280, those with the earlier method, by 100. Thus the upper limit of normal is 1.0.

(CCl_4, C_6H_6, CH_3Cl, and others). In Figure 2 a definite contrast is evident between the UCP isomer ratios in the refractory anemias versus hemolytic, pernicious, and hypochromic anemias. The difference is highly significant (P = 0.001). It is unknown at present whether the moderate increases of urinary coproporphyrin III in the refractory anemia cases are a direct result of a mild residual chemical intoxication or whether they are due to a faulty heme synthesis which is an expression of bone marrow or liver injury. Such an injury might well be ascribed to chemical exposure, a history of which is often obtained in these cases.[43,44]

It is interesting that in the majority of cases of leukemia this reversal of UCP isomer ratio has not been observed (Fig. 2). It is seen that increase of the total UCP is quite inconstant. Nevertheless there are some remarkable exceptions which are not well understood. In certain instances an outspoken history of chemical exposure, well in advance of the first symptoms of leukemia, has suggested a causal relationship both with the leukemia and the excessive

urinary Type III coproporphrin. The following case is an example.

Leukopenic myeloid leukemia clinically simulating aplastic anemia; benzene poisoning?

Weakness, pallor, recurrent infections; history of using a grain spray containing benzene for two years. No palpable lymphadenopathy; spleen and liver not palpable. Laboratory findings were as follows: Hgb., 6.6 gm./100cc.; RBC, 1.8 million; WBC, 1300, with 16% Neutrophiles and 83% lymphocytes. Bone marrow showed probable subacute myeloid leukemia; confirmed at necropsy (liver and spleen). UCP was 116γ/day, 80% Type III; FCP, 709 γ/day 66% Type III; feces urobilinogen, 390 mg/day.

It is of interest in the above case that the total urinary coproporphyrin was well within the normal range, yet there was marked preponderence of the Type III isomer. This was also true in the feces.

In certain other cases of leukemia with a reversed isomer ratio (Fig. 2), no such history has been obtained. In Hodgkin's disease a reversal of the isomer ratio is not uncommon, indeed, marked excesses of coproporhyrin III are rather often observed (Fig. 2). The difference in this respect between Hodgkin's disease and leukemia appears to be significant ($P = 0.007$). One possible explanation for this difference is the much greater frequency of necrosis in Hodgkin's disease than leukemia. This would suggest, in other words, that an endogenous chemical toxicity may be the factor of significance, but it is recognized that there may be other more important factors. It should be emphasized that careful analysis of our cases has failed to reveal correlation with fever, neutrophilia, or toxic changes in the leukocytes, or other manifestations which might suggest such a toxicity.

In the time allotted a more comprehensive discussion of the subject is scarcely feasible, and indeed our knowledge, at least from many standpoints, is still too fragmentary to permit this. In the foregoing the "dualism" of the porphyrins, as first postulated by Hans Fischer,[45] i. e., the occurrence of isomer Types I and III, has been given considerable place. It is recognized, however, that Types II and IV are not distinguished from I and III, respectively, by the micromethods which have been employed for the distinction of isomers, such as the fluorescence quenching technique[34] and the Chu-Green paper chromatographic method.[35] Isolation of the crystalline methyl esters for melting point determination is of value, but cumbersome, and may fail to yield information as to possible significant moieties of other isomers that may remain in the mother liquors. The infrared spectrophotometric (microscopic) method permits excellent distinction of the four coproporphyrin isomers with as little as 20γ of each. However, this applies to pure material, and some difficulty has thus far been encountered in attempting to resolve mixtures which have been purified chromatographically but not crystallized. Data obtained with this method thus far indicate that under certain circumstances significant amounts of the Type II or IV isomers are excreted, at least in some cases of porphyria. It appears unlikely, however, that the amounts will often be of great importance.

In closing may I acknowledge again the keen sense of privilege that has been mine in giving the George Minot Lecture for 1956 to your Section on Experimental Medicine and Therapeutics.

Addendum

Since presentation of this paper, Shemin and Rosenblum[50] have reported incorporation of C^{14}-labelled δ-aminolevulinic acid in vitamin B_{12} formed by Streptomyces griseus.

Goldberg and co-workers[51] have recently reported inhibition of heme synthesis by lead, as studied with Fe^{59} and chicken red cell hemolysate. The inhibition was present at several levels, more marked at the formation of δ-aminolevulinic acid, and at the incorporation of iron into protoporphyrin.

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§ This study is in progress with Dr. Marie Berg.

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Therapeutic Considerations in Chronic Lymphocytic Leukemia

Special Reference to the Natural Course of the Disease

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The alarming diagnosis of leukemia is apt to result in profound emotional disturbances in the patient and his family. The serious implications of leukemia in general frequently overshadow the relatively benign nature of many cases of chronic lymphocytic leukemia. This occasionally leads to vigorous treatment wherein the risks of profound marrow depletion may not be properly weighed against the objectives of therapy. Also, chronic lymphocytic leukemia, occurring as it does in the elderly, is frequently erroneously implicated as responsible for symptoms of other degenerative and neoplastic diseases which happen to be independently present in the same patient. For these reasons, knowledge of the natural course of the disease is necessary as prerequisite for its intelligent management.

Previous studies suggest a prolonged course in chronic lymphocytic leukemia,[1-5] but there are few reports relative to the rate of progression of symptoms and signs in these patients. The occasional appearance of case reports which deal with an exceptionally long life span in chronic lymphocytic leukemia imply that such events are exceptional.[6-8] On the other hand, in a recent symposium on the management of chronic lymphocytic leukemia[9] a panel of authorities concurred that a rather benign course is usual in this disease. It follows, therefore, that these cases should be handled by watchful expectancy, with active therapy reserved for more aggressive forms of lymphocytic leukemia. There is no uniform opinion as to the over-all influence of therapy on the development of chronic lymphocytic leukemia.

The purpose of this study is to document the natural course of this disease in order to provide a guide to the application of specific myelodepressant or antileukemic therapy.

Clinical Data

The clinical records of 86 patients with the diagnosis of chronic lymphocytic leukemia from 1946 to 1956 were examined. All cases were seen personally by one or both of the authors. Thirty-four patients were seen during a single and frequently terminal hospitalization. The other 52 were followed as hospital and outpatients for periods exceeding six months and frequently over many years.

In these patients our interest was specifically directed to progression of symptoms directly attributable to leukemia; changes in size of lymph nodes, spleen, and liver; changes in blood cell counts, and systemic evidence of progression of the disease.

The diagnosis was confirmed by hematologic study in all patients and by bone marrow examination in 67 of the group. The criteria for diagnosis included leukocytosis with absolute lymphocytosis and a monotonous bone marrow picture which showed preponderance of mature lymphocytes. In three patients, the leukocyte and differential counts were normal; the diagnosis of chronic lymphocytic leukemia was made by repeated marrow-aspiration biopsies.

The course of chronic lymphocytic leukemia, in this group of patients, arranged itself into three basic patterns:

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1. The first category showed a relatively stationary or slightly progressive activity. In 62 patients, the leukemia appeared to coexist peacefully with the patient.

2. In the second group, there was progressive increase in the size of lymph nodes, liver, and spleen, together with systemic symptoms such as progressive cachexia, fever, and weight loss. Eighteen patients mainfested this type of disease, which appeared to share the malignant features of leukemia and lymphosarcoma.

3. In six patients the clinical picture was dominated by the complicating autoimmune hemolytic anemia. This was characterized by profound anemia with evidences of regeneration, icterus, splenomegaly, and a positive antiglobulin reaction.

Age and Sex Incidence

Data on age and sex distribution are presented in Figure 1. There were 56 men and 30 women. Breakdown of the age incidence confirms that this is a disease of old age, as 85% of our patients were over 60 years of age, both men and women. The youngest patient was 25 and the oldest 89 years of age, and the average age was 71 in Group I, 61 in Group II, and 68.8 in Group III.

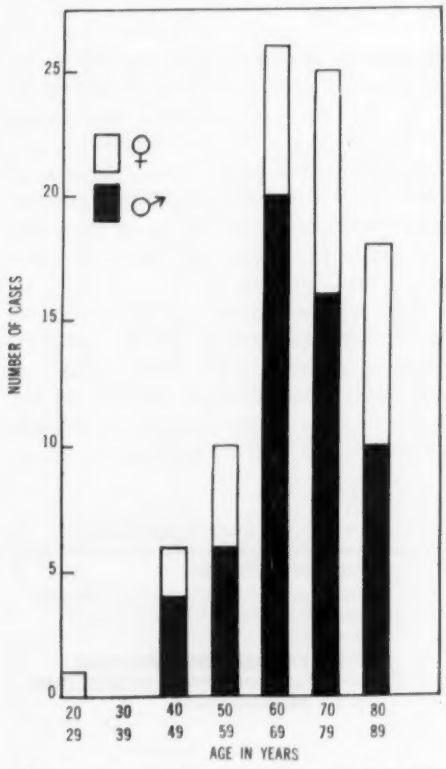

Fig. 1.—Age distribution of 86 cases of chronic lymphocytic leukemia.

Duration and Survival

Of 86 cases of chronic lymphocytic leukemia, 54 are dead and 20 are alive. The status of 12 remaining patients is unknown. It is presumed that most of these are dead, since these patients were hospitalized several years ago and, for a variety of reasons, were lost to observation. Duration of disease may be calculated either from the time of the first symptoms attributable to leukemia or from the time when the diagnosis was definitely established. Neither offers a precise method of reckoning the onset. For one thing, hematologic changes may be present for a variable period of time before symptoms or outward signs may occur. Also, the presence of more than one chronic disease, in a patient with leukemia, leads to confusion as to which disease may be responsible for the patient's incapacitation.

These points are considered in Figure 2. In the benign group of leukemias, symptoms were few and if present were frequently attributable to another accompanying disease. In 50 cases (58%), chiefly composed of Group I patients, leukemia was an incidental finding in the routine blood examination when patients were first examined. In this group, medical attention was sought for a variety of disorders, including congestive heart failure, coronary artery disease, Buerger's disease, pneumonia, carcinoma, trauma, acute abdominal emergencies, diabetic control, and other disorders frequently encountered in this age group. Symptoms in these patients were related to the accompanying disease and included weight loss (in those patients with carcinoma), precordial pain, backache, abdominal pain, intermittent claudication, gangrene of extremities, polydypsia, frequency of urination, nocturia, and others.

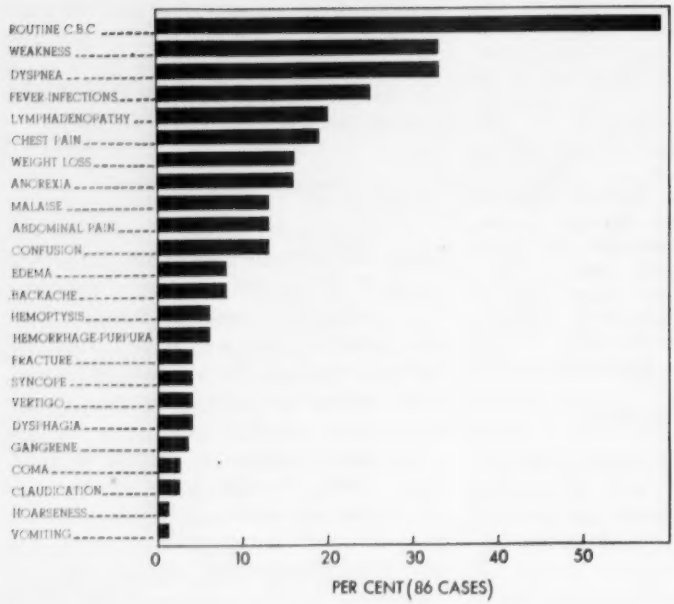

Fig. 2.—Symptoms on admission of 86 cases of chronic lymphocytic leukemia.

The most frequently encountered symptoms were weakness and dyspnea (32% each). These symptoms could arise from anemia (which was significant in only two patients with "benign" leukemia), but were difficult to explain in the presence of a normal red cell count. It was more likely that, in most instances, weakness and dyspnea arose from another incidental disorder, such as congestive heart failure, coronary insufficiency, chronic bronchitis, and other afflictions of old age. In 25% of patients, the diagnosis of chronic lymphocytic leukemia was established during an admission for an infectious disease, such as bronchopneumonia or pyelonephritis.

The "aggressive" leukemias, though morphologically similar, behaved clinically almost as another disease. Because of the pronounced symptomatology of this group, these patients had been under sustained medical observation for a longer period of time. Hence, it was possible to fix the time of onset of symptoms, which included fever, malaise, weakness, weight loss and progressive, painless lymphadenopathy. Splenomegaly and hepatomegaly were frequently pronounced in this group as opposed to the patients of Category I (Table 1 and Fig. 3).

In the six patients with autoimmune hemolytic disease, the first symptoms were those of anemia in all cases. In two of these patients the presence of leukemia was already known by routine blood cell count for one to two years, and hemolysis was a later complication.

On the other extreme of the course of chronic lymphocytic leukemia, the variability of cause of death in 54 patients (Table 2) also made a statement of duration of leukemia inexact. Twenty-three patients (43% of those dead) died for a variety of reasons

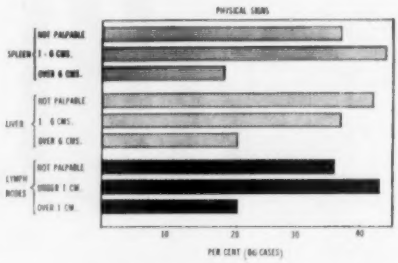

Fig. 3.—Physical signs of 86 cases of chronic lymphocytic leukemia.

TABLE 1.—*Clinical Data on Fifty-Two Patients Followed for More Than Three Months*

Relatively Benign

Case No.	Age Sex	Initial Findings: Duration, Yr.	Spleen, Cm.	Liver, Cm.	Lymph Nodes, Cm.	RBC, Millions/Cu. Mm.	WBC/Cu. Mm.	Platelets/Cu. Mm.	Lymphocytes, %	Therapy	Late Findings: Duration, Yr.	Spleen, Cm.	Liver, Cm.	Lymph Nodes, Cm.	RBC, Millions/Cu. Mm.	WBC/Cu. Mm.	Platelets/Cu. Mm.	Lymphocytes, %	Outcome
1	82-M	0	0	0	0	3.34	18,200	194,000	87	None	1.5	0	0	>1	3.01	16,100	..	95	Dis.; no follow-up
2	75-F	0.2	6	6	0	3.21	46,000	184,000	99	None	0.5	6	6	>1	3.37	36,000	..	98	Died fract. hip-bronchopn.
3	80-F	1.0	12	6	>1	4.04	116,200	69,000	91	X-ray	1.3	..	..	..	2.9	128,200	150,000	96	Died fract. hip-bronchopn.
4	77-F	0	0	0	0	3.29	98,500	160,000	93	None	1	0	0	0	2.8	42,000	397,000	68	Cancer rectum; no follow-up
5	63-M	0	0	4	0	..	17,000	..	60	None	3	6	6	0	Hb.15	16,100	..	63	Disch.; no follow-up
6	70-M	0	0	Huge	0	4.19	87,400	..	86	X-ray, HN:	0.3	1	8	0	3.13	5,300	143,000	39	Died Pneumonia
7	63-M	0.8	4	8	2	Hb.13.5	25,700	184,000	80	None	1	0	Huge	2	3.07	98,000	..	88	Died cancer lung
8	67-M	0	0	0	0	4.5	75,000	216,000	75	X-ray	3	4	8	0	5.53	33,700	186,000	44	Died cong. ht. failure
9	65-F	3	0	0	0	3.81	6,000	..	32	None; later TEM	5	4	8	0	2.10	1,700	8,000	89	Died aplastic crisis
10	76-F	7	6	6	0	2.00	5,500	53,000	69	None	2.8	4	4	0	3,4	3,700	84,000	67	Alive, "occult" hemolytic anemia
11	80-M	0	0	0	0	3.32	19,600	77,000	70	None	1.5	0	10	0	4.87	39,200	..	81	Died heart disease
12	63-F	0	0	0	0	Hb.15	19,800	..	52	None	9	2	0	0	5.54	97,600	192,000	64	Died ruptured appendix
13	81-M	28	0	0	0	4.50	43,700	..	81	X-ray	35	4	1	>1	4.32	25,000	65,000	84	Died cancer stomach
14	62-M	3	0	0	>1	5.0	19,000	..	75	None	4	2	0	>1	5.3	50,400	..	84	Alive; silicotuberculosus
15	76-M	0	0	0	0	3.23	12,600	..	17	None	2	0	0	0	3.74	6,100	..	9	Died bronchopn.
16	83-F	0	0	0	0	3.77	22,000	..	69	None	1	0	0	0	2.70	62,200	212,000	77	Alive
17	79-M	0	0	4	>1	Hb.12.5	9,400	..	86	None	2	1	0	2	3.40	27,000	258,000	90	Died Bronchogenic cancer
18	67-F	3	0	0	0	4.45	53,400	..	74	X-ray, TEM, CB 1348, cortisone	15	8	4	2	3.0	400,000	20,000	100	Died C.L.L.
19	66-M	0	0	0	0	4.68	139,000	..	83	Urethan	0.5	0	0	0	3.97	50,500	246,000	88	Died pneu. meningitis
20	44-F	0.5	4	8	0	2.82	155,200	64,000	83	Urethan	0.6	..	..	..	2.42	36,000	..	82	Died pneu. septicemia
21	77-F	0	0	0	0	Hb.13	24,100	..	77	None	Transferred to nursing home								Alive, no follow-up
22	65-M	0	1	6	2	3.77	34,700	214,000	77	None	Moved out of town								Alive, pos. Coombs'; not followed
23	76-M	0	1	0	>1	4.40	70,500	..	92	None	4	0	0	0	3.2	32,500	..	88	Died cancer Urinary bladder
24	54-F	2	1	4	4	5.33	6,000	146,000	39	TEM	4	0	0	1	Hb.13	15,200	..	45	Died C.V.A.
25	72-M	0.8	2	4	>1	4.18	59,800	189,000	98	TEM, CB 1348	3.5	4	0	1	3.09	69,000	..	95	Alive
26	49-F	0.5	0	0	4	4.90	38,000	216,000	78	X-ray	1.5	4	0	2	4.13	54,000	134,000	89	Alive
27	45-M	2	0	0	2	4.5	33,800	..	82	X-ray, CB 1348	3	0	0	2	4.51	166,400	114,000	69	Alive
28	56-F	2	0	2	1	4.29	18,800	..	52	CB 1348	4	4	0	2	4.69	23,000	80,000	75	Alive
29	70-M	0	4	2	3	4.64	22,700	116,000	87	None	1	2	6	2	Hb.10.9	9,000	..	62	Alive, cancer kidney
30	65-F	8	8	8	3	4.1	16,700	92,000	90	TEM, prednisone, CB 1348	10	8	8	2	3.86	37,600	150,000	90	Alive

TABLE 1.—*Clinical Data on Fifty-Two Patients Followed for More Than Three Months*—Continued

Case No.	Age Sex	Initial Findings: Duration, Yr.	Spleen, Cm.	Liver, Cm.	Lymph Nodes, Cm.	RBC, Millions/Cu. Mm.	WBC/Cu. Mm.	Platelets/Cu. Mm.	Lymphocytes, %	Therapy	Late Findings: Duration, Yr.	Spleen, Cm.	Liver, Cm.	Lymph Nodes, Cm.	RBC, Millions/Cu. Mm.	WBC/Cu. Mm.	Platelets/Cu. Mm.	Lymphocytes, %	Outcome
										Aggressive Leukemia									
31	81-F	2	2	2	0	1.19	296,000	..	96	2 trans.	2.2	2	2	0	1.64	222,000	..	92	Died hemolytic anemia
32	70-F	1	8	10	0	4.30	27,300	..	81	------	1.6	8	12	0	3.81	127,000	290,000	73	Died pneumonia
33	61-M	0	10	10	>1	1.49	496,000	22,000	98	X-ray	0.2	10	6	>1	3.28	90,000	23,000	98	Disch.; no follow-up
34	59-M	8	Huge	2	>1	3.76	194,000	26,000	93	X-ray, urethan	9	Huge	4	>1	2.33	5,500	39,000	52	Disch.; no follow-up
35	69-M	0.4	..	4	4	..	19,500	..	..	X-ray	0.5	..	6	2	2.95	77,000	36,000	93	Died myocardial infarction
36	45-M	1	12	6	4	6.5	24,200	97,000	45	X-ray, TEM	4	Huge	0	3	3.10	41,500	..	84	Died C.L.L.; cancer larynx
37	25-F	10	8	4	1	2.62	4,000	58,000	81	ACTH	12	10	1	2	3.7	87,200	26,000	93	Died C.L.L.
38	83-F	1	10	8	3	3.32	232,000	64,000	97	TEM	2	10	10	4	3.0	16,800	86,000	93	Died C.L.L.
39	64-M	0	0	4	0	6.51	11,200	178,500	57	X-ray	3.2	17	4	>1	2.4	123,600	..	90	Died C.L.L.; "blast crisis"
40	67-F	3	8	6	6	2.45	627,000	38,000	99	X-ray	4	18	6	4	3.07	303,000	13,000	99	Died C.L.L.
41	58-M	0.3	6	10	4.6	3.80	190,000	187,000	96	Urethan	0.4	16	10	6	3.71	283,000	..	98	Died C.L.L.
42	48-M	2	Huge	Huge	2-4	5.70	11,700	..	47	X-ray	2.4	Huge	Huge	2-4	3.98	2,400	174,000	40	Died C.L.L.
43	68-M	1	14	7	4	4.26	62,000	94,000	92	CB 1348	1.5	6	8	2	3.26	11,400	..	70	Alive
44	45-M	2	8	2	2	4.19	114,000	148,000	89	TEM, Cortisone, x-ray	2.5	12	11	2	3.74	228,000	..	92	Died extreme facial edema (lymphatic obstruction?)
45	64-M	2	0	6	0	1.68	181,000	34,000	97	Cortisone	3.5	2	2	0	1.39	87,200	13,000	90	Died purpura, progressive asthenia
46	69-M	1	4	0	2	3.74	297,000	186,000	97	CB 1348	1.5	4	4	>1	3.05	126,400	56,000	96	Alive
										Hemolytic Anemia									
47	68-F	0.6	6	4	2	1.45	171,000	184,000	98	X-ray, splenectomy	1.6	..	..	1	0.780	358,000	266,000	99	Died Hemolytic crisis
48	70-M	0.1	10	0	2	1.50	417,000	68,000	96	Trans.	0.1								Died hemolytic crisis
49	84-M	0.1	6	8	>1	2.84	279,000	102,000	88	Trans. CB 1348	0.4	8	2	71	1.68	97,000	..	79	Died hemolytic crisis
50	65-M	0	8	8	>1	Hb.14	174,600	..	92	X-ray, cortisone, prednisone	3	4	6	0	4.10	54,600	..	92	Alive
51	55-M	2	4	0	0	3.25	9,200	78,000	80	Cortisone	3	6	0	0	2.65	18,500	62,000	74	Alive
52	71-F	1	6	0	>1	3.37	256,500	..	99	Prednisone, CB 1348	1.5	4	0	2	2.67	38,000	74,000	97	Alive

TABLE 2.—*Causes of Death of Fifty-Four Patients with Chronic Lymphocytic Leukemia*

I.	Chronic lymphocytic leukemia				20
	Progressive debility			6	
	Lymphosplenomegaly			6	
	Hemolytic crisis			3	
	Thrombocytopenia			2	
	"Blast" crisis			1	
	Aplastic crisis (TEM)			1	
	Adrenocortical insufficiency			1	
II.	Carcinoma				9
	Bowel	2	Prostate	1	
	Lung	2	Stomach	1	
	Ur. Bladder	2	Larynx	1	
III.	Heart disease—Arteriosclerosis				7
	Cong. heart failure			3	
	Myocardial infarction			2	
	Cerebral thrombosis			1	
	Buerger's disease			1	
IV.	Infection				5
	Pneumonia			4	
	Tuberculosis, rupt. appendix			1	
V.	Miscellaneous				13
	Intest. obstruction			1	
	Scurvy—malnutrition			1	
	Unknown			11	
	Total				54

not of leukemic nature. Nine of these patients had carcinoma which was primary in the bowel,[2] the lung,[2] the urinary bladder,[2] the prostate, the larynx, and the stomach (1 each). Seven patients died of heart disease. Three of these had congestive heart failure, two with myocardial infarction, one with cerebral thrombosis, and one with Buerger's disease and gangrene. Five patients died as result of infection. In four patients with pneumococcic pneumonia (one with meningitis and one with septicemia) it was possible that the debilitated state and immunologic abnormality associated with lymphocytic proliferation made these persons extraordinarily susceptible to the pneumococcus. In the remaining patient, death occurred because of a ruptured appendix.

In 21 patients (39%), death was directly or indirectly attributable to leukemia. Broken down further, this included progressive debility with enlargement in lymph nodes and spleen in six patients who bore the clinical features of both chronic lymphocytic leukemia and lympsosarcoma (leukosarcoma). Three patients died in hemolytic crisis during the course of autoimmune hemolytic anemia in which the antiglobulin test was positive. In these instances, one patient died nine months following splenectomy. One died about a month following excellent remission in both leukemia and hemolytic anemia treated with chlorambucil (CB 1348), and one was terminal on his first admission to the hospital. Only one patient in the entire series died in "blast" crisis, a situation not infrequently seen in chronic granulocytic leukemia. Two patients died because of progressive thrombocytopenia and anemia with associated hemorrhage and debility. One patient died in aplastic crisis which had followed the administration of 10 mg. of triethylenemelamine. One patient died in another hospital rather suddenly following treatment with x-ray. This man, who had developed far-advanced edema of the face, presumably due to lymphatic blockade, was autopsied, but no explanation for the sudden death could be found. Our youngest patient (29 at time of death) died suddenly after a prolonged course of cortisone. It was likely that her death represented adrenocortical insufficiency. Eleven patients died away from the hospital, cause unknown.

Because of uncertainty in time of onset and because the cause of death in our cases was frequently another incidental disease, we did not attempt to analyze the factors which influenced total duration of chronic lymphocytic leukemia. For these reasons, wherever it was possible to achieve prolonged follow-up, the cases were studied for rate of progression of signs and symptoms.

Course of Chronic Lymphocytic Leukemia

Table 1 is a summary of the chief clinical and hematologic features, approximate duration, treatment, and outcome in 52 patients in whom follow-up was possible for a period long enough to establish the trend of the disease. For the purpose of this part of the study, those patients that were seen during a single hospitalization or outpatient visit were omitted. Limitation of space does not permit details of the course of all the patients in this series.

The initial findings are those elicited on the very first hospital or outpatient visit as close as possible to the original date of diagnosis. The late findings are intended for comparison and, as a measure of activity of leukemia, were found on the most recent examination of the patient or shortly before death.

In Group I, composed of 30 patients, the known duration of leukemia ranged from 1 month to 35 years. Six patients were followed for a short period of time. Cases 19 and 20 were under observation for only one month and died during this hospitalization of pneumococcal septicemia. It could not be established how long these patients had chronic lymphocytic leukemia, as there were no symptoms of this disease. A course exceeding three years was seen in seven men and seven women. (Cases 5, 8, 9, 10, 12, 13, 14, 18, 23, 24, 25, 27, 28, and 30.) The spleen, liver, and lymph nodes were small to begin with. At the onset, the spleen was not palpable in 19 patients, extended less than 6 cm. below the costal margin in 9 patients, and exceeded 6 cm. below the costal margin in only 2 patients. At the conclusion of follow-up study, the spleen remained impalpable in 10 patients, under 6 cm. in 14, over 6 cm. in 2, and was not recorded in 4. Lymph nodes were not palpable in 17 patients, measured less than 2 cm. in 9, and over 2 cm. in 4 patients. During the course of illness, there was slight change in the size of nodes, and they remained impalpable in 12, under 2 cm. in 14, and not recorded in 4.

In this group, significant anemia (under 3,000,000/cubic millimeter) was encountered in only two patients. One of these patients (Case 10) had, at the onset, extensive marrow infiltration and an occult or "hemopathic" hemolytic component, and the other patient (Case 20) had pneumococcal septicemia. Anemia developed late in the course of chronic lymphocytic leukemia in five patients. Two of these were the patients mentioned above, the other three were an 80-year-old woman (Case 3) with a fractured hip, a 77-year-old woman (Case 4) with carcinoma of the rectum, and a 65-year-old woman (Case 9) who developed aplastic anemia following treatment with triethylenemelamine (TEM).

In most cases, the reticulocyte and platelet count were normal, but slight to moderate thrombocytopenia without clinical bleeding was present in five patients (Cases 3, 10, 11, 20, and 30). There was no drop in the number of platelets save for Patients 9 and 18, in whom thrombocytopenia was attributable to therapy (chlorambucil and triethylenemelamine). The leukocyte count was under 100,000 in all cases except for Cases 3, 19, and 20, all three of whom had severe pulmonary infections at the time of admission. Increases in the number of leukocytes, suggesting progressive leukemic activity, were encountered in Cases 18, 25, and 27. In cases followed over many years, the progressive increase in leukocyte count may represent increase in the life span of lymphocytes rather than overproduction. This is suggested by the independent observations of Weisberger, Suhrland, and Levine,[10] Hamilton,[11] and Osgood and his group,[12] who found that the life span of lymphocytes in chronic lymphocytic leukemia varied from 30 days to a year. In one woman (Case 12), followed for 9 years, the number of leukocytes had remained under 50,000 for the entire course of her final admission for a ruptured appendix with peritonitis. The leukocyte count exceeded 115,000 per cubic millimeter for the first time when the infection occurred.

A brief consideration of the course of several typical patients of this group seems in order at this point. One man (Case 13, Fig. 4) was found to have chronic lymphocytic leukemia by routine blood cell count when he was accidentally electrocuted in 1920. In 1932 and 1948, because of projectile vomiting associated with pyloric obstruction, he received radiation therapy to the epigastrium, each time with relief of symptoms. On his final admission, at the age of 88, surgery was necessary to relieve

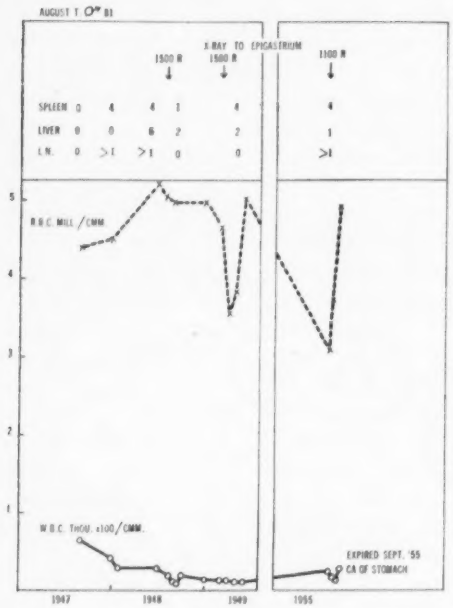

Fig. 4.—Summary of Case 13.

pyloric obstruction, and carcinoma of the stomach was found, from which he died one month later. At no time during this man's illness was there any evidence of progression of the leukemic process. The spleen, liver, lymph nodes, and blood cell counts all remained of the same magnitude throughout.

A woman (Case 18, Fig. 5) was followed for 12 years, during which time there was little clinical evidence of leukemia. In 1951 and 1952 she was hospitalized because of tuberculosis. A year later there was increase in the leukocyte count and in the size of nodes and spleen and progressive asthenia

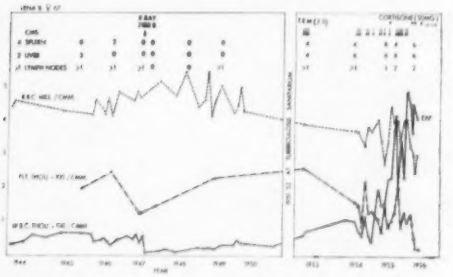

Fig. 5.—Summary of Case 18.

unresponsive to therapy with triethylenemelamine or chlorambucil. She developed a positive antiglobulin test and hemolytic anemia, successfully treated with cortisone and prednisone. However, osteoporosis and pathologic fracture of the spine occurred. This patient died at least 15 years after the diagnosis of chronic lymphocytic leukemia was established. This case is of some interest in light of the findings of Moffitt and Lawrence [5] that of 16 patients with chronic lymphocytic leukemia of greater than five years' duration, only one was a woman. Despite the relative benignity of this group of cases, progression of signs, when present, is a clear-cut indication for therapy. One man, age 72 when first seen, (Case 25, Fig. 6) showed a slow but decided increase in

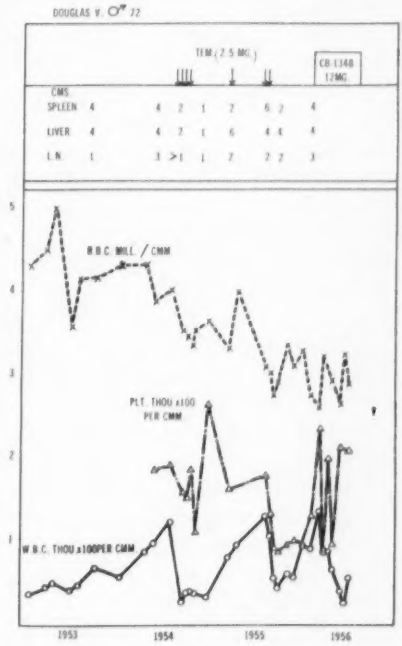

Fig. 6.—Summary of Case 25.

the size of lymph nodes and spleen and in the leukocyte count, with a gradual drop in the number of erythrocytes. These objective findings responded fairly well to small doses of triethylenemelamine and later chlorambucil, but the disease continued to

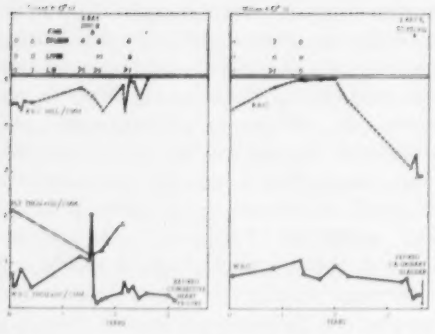

Fig. 7.—Summary of Cases 8 and 23.

progress despite treatment. In 11 patients (Cases 2, 3, 6, 7, 8, 11, 15, 17, 19, 20, and 23) death occurred before the leukemic process had sufficient opportunity to bring forth symptoms. This is illustrated in Figure 7, which illustrates two patients (Cases 8 and 23) with relatively stationary leukemia but who died of congestive heart failure and of carcinoma of the urinary bladder, respectively.

The 16 patients in Group II showed a more aggressive, and therefore more serious, form of chronic lymphocytic leukemia. These cases were all characterized by pronounced and severe symptoms: fever, malaise, weakness, weight loss, and other systemic symptoms. Because of the pronounced symptomatology of this group, they had been under medical care for a longer period of time. Hence, it was possible to calculate duration of illness in many of these cases from the time of onset of symptoms, which ranged from 5 months, in a patient that suffered an acute myocardial infarction (Case 35), to 12 years, in a young woman (Case 37) who was in constant difficulty during the latter years of her illness with anemia and thrombocytopenia. The average duration in this group was 3.2 years.

Of the 16 patients in this group, the spleen exceeded 6 cm. below the costal margin in 11 instances (Cases 32, 33, 34, 35, 37, 38, 40, 41, 42, 43, and 44), and the lymph nodes were greater than 2 cm. in 9 patients (Cases 35, 36, 38, 40, 41, 42, 43, 44, and 46). Although these organs regressed temporarily with treatment, in some cases, progressive enlargement was the rule during the time that therapy was not administered. Significant anemia (under 3,000,000) was present at the onset in four patients (Cases 31, 33, 37, and 40) and in five instances following the period of observation (Cases 31, 34, 35, 38, and 39). However, every patient in this group, except Cases 33, 37, and 40, showed a significant drop in erythrocytes during the course of disease. There was great variation in the leukocyte count, which ranged from 4000 to 627,000. With two exceptions (Cases 36 and 37), the leukocytes exceeded 100,000 at least once during the course, and, in many instances, this extreme leukocytosis persisted for the entire course. Thrombocytopenia was present at the onset in eight patients (Cases 33, 34, 36, 37, 38, 40, 43, and 45) but resulted in serious bleeding in only two (Cases 37 and 45).

One unusual patient (Case 39, Fig. 8) was found to have chronic lymphocytic leukemia during hospitalization for coronary

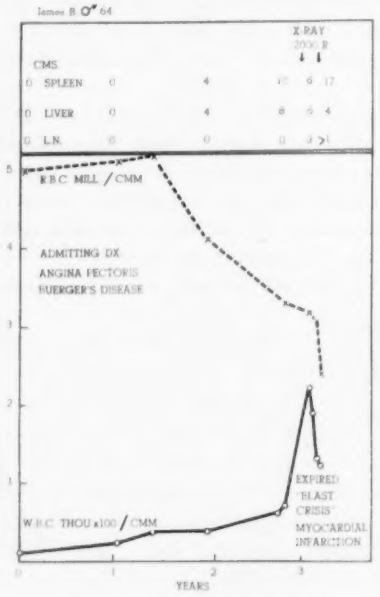

Fig. 8.—Summary of Case 35.

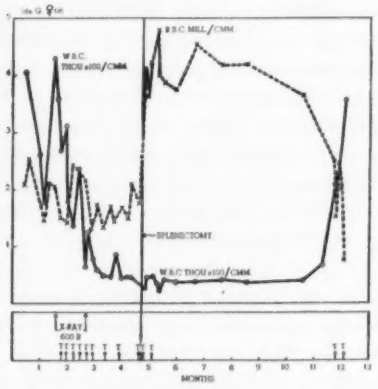

Fig. 9.—Summary of Case 47.

insufficiency. The disease seemed to have benign characteristics, and specific therapy was not given. However, two years after the diagnosis of chronic lymphocytic leukemia was established, progression of splenomegaly began, and shortly before the patient died, one year later, there was a great increase in the number of lymphoblasts in the peripheral blood and marrow. This so-called "blast crisis," the only one encountered in this series of chronic lymphocytic leukemia, is not unusual as a terminal state in chronic granulocytic leukemia.

The remaining six patients were all profoundly anemic and slightly icteric and had an enlarged spleen with slight lymphadenopathy. There was reticulocytosis, a positive antiglobulin test, increase in fecal urobilinogen excretion, and diminished erythrocyte survival, which identified antoimmune hemolytic anemia.[13] Of these six patients, three are dead and three are alive. One woman (Case 47, Fig. 9) was originally treated with radiation, which resulted in regression

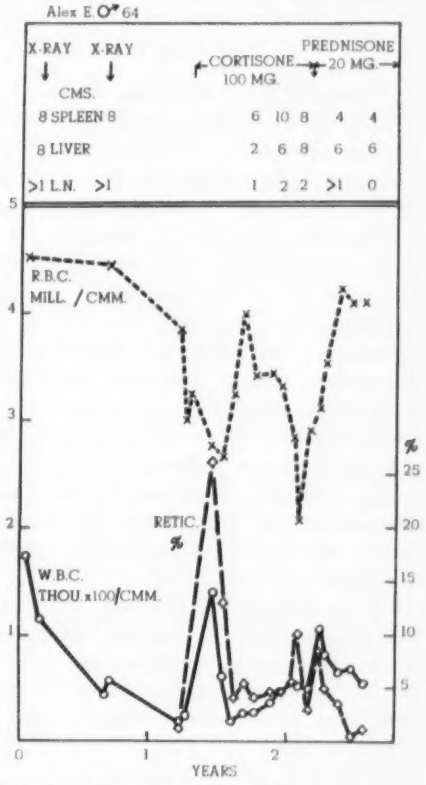

Fig. 11.—Summary of Case 50.

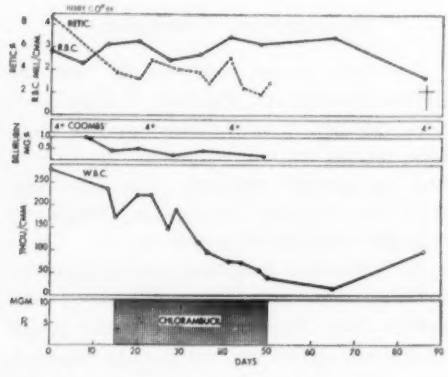

Fig. 10.—Summary of Case 49.

of the leukocyte count, the nodes, and the spleen, but no effect on the hemolytic process. Splenectomy was followed by remission for seven months, but a sudden hemolytic crisis claimed the life of this woman. One man was treated solely with chlorambucil (Case 49, Fig. 10). The leukemia was brought under control, and with it hemolysis ceased, but when this drug was discontinued a sudden hemolytic crisis resulted in this patient's death. One patient was admitted to the hospital in terminal hemolytic crisis, and the other three are alive and reasonably well following therapy with the steroid hormones. A typical response to cortisone

and prednisone is illustrated in Figure 11 (Case 50). In two patients, it has not yet been necessary to administer antileukemic therapy, but the third was recently started on chrorambucil because of increasing leukocytosis and splenomegaly.

Comment

The existence of chronic lymphocytic leukemia of exceptionally long duration is well known. Moffitt and Lawrence [5] state that merely pointing out this fact offers no explanation for the prolonged course, nor is it possible to predict in advance which cases will belong to this chronic variety. We agree that there can be no accurate prognostic rule of thumb in a disease as unpredictable as leukemia. However, our observations suggest that pronounced splenomegaly, lymphadenopathy, and anemia and significant leukocytosis all portend an unfavorable course in leukemia. On the other hand, a relatively small spleen and lymph nodes, a normal erythrocyte and platelet count, and moderate leukocytosis suggest an intrinsically benign disease.

Specific therapy for leukemia will probably not be available until we learn more of the secrets of uncontrolled cell growth and of etiologic factors. There is some doubt that present-day therapeutic agents actually prolong the life of the patients. Their greatest use is to prolong useful life by diminishing symptoms. Obviously, palliation is administered to best advantage only in the presence of well-marked symptoms. For this reason, it is inadvisable to give irradiation or powerful myelodepressant drugs to the patient with intrinsically benign disease unless well-marked progression can be demonstrated.

Progression is suggested by the presence of such symptoms as fatigability, malaise, dyspnea, chills, fever, anorexia, and weight loss (keeping in mind that these complaints are encountered in many clinical states). The aggressiveness of the leukemic process is further checked by increase in size of lymph nodes, spleen, and liver; a steady increase in the number of leukocytes, and a fall in the erythrocytes and platelets, which should be counted every three or four months (Dameshek [9] says that more frequent counting might aggravate leukemic neurosis). Finally, the routine management of a patient with chronic lymphocytic leukemia should include a Coombs' antiglobulin test, reticulocyte determination, and serum bilirubin, performed every six months to rule out autoimmune hemolytic anemia.[13]

Should active treatment be necessary, the choice lies between roentgen therapy and chemotherapy. Radiation seems to be better appointed for the patient with large localized masses of nodes and massive splenomegaly, where disappearance of unsightly tumor masses is desirable. Effective chemotherapeutic agents include triethylenemelamine and, now, chlorambucil, which has shown great promise in our clinic. Corticotropin (ACTH) and cortisone are of greatest value in the treatment of autoimmune hemolytic anemia [13] but may also be employed for their myelostimulatory properties, in purpura, and for their lympholytic action.[14]

Finally, an important consideration in therapy is to seek and treat the associated disease which so frequently is present. This includes all of the neoplastic diseases and degenerative disorders that befall old age and that are encountered so frequently in conjunction with chronic lymphocytic leukemia.

Summary and Conclusions

A review is presented of 86 cases of chronic lymphocytic leukemia. Fifty-two of these patients were followed over a long-term period in our outpatient department and as hospital patients. The remainder were seen during a single, and frequently terminal, hospital admission.

It is possible to group chronic lymphocytic leukemia into three well marked categories: (*a*) Benign, in which the lymph nodes and spleen are not greatly enlarged, the erythrocytes and platelets are normal,

and the leukocyte count frequently under 100,000/cubic millimeter; (*b*) progressive, in which there is increase in the size of lymph nodes and spleen, frequently with systemic involvement, anemia, pronounced leukocytosis, and thrombocytopenia; (*c*) autoimmune hemolytic disease, with profound anemia, reticulocytosis, splenomegaly, and a positive Coombs' antiglobulin reaction.

Chronic lymphocytic leukemia is frequently accompanied by another neoplastic or degenerative disease which may dominate the clinical picture and take therapeutic precedence.

The treatment of chronic lymphocytic leukemia depends upon the activity of the disease, the degree of symptomatology, and the presence of associated disease.

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Vitamin B_{12} and Iron Deficiencies in Anemia of Pregnancy and Puerperium

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Anemia in pregnant women is common particularly in countries where the birth rate is high and malnutrition prevalent. This anemia may be hypochromic due to iron deficiency or may be of the type variously referred to as macrocytic, hyperchromic, megaloblastic, or pernicious anemia of pregnancy. This classification is based on the morphological changes in the peripheral blood and bone marrow and on the response to therapy. In the case of hypochromic anemia the therapeutic response to iron is usually clear-cut, justifying its classification as an iron-deficiency anemia. In the macrocytic anemia of pregnancy, however, the therapeutic response is variable, and this type of anemia has been found to respond to a variety of substances, including crude and refined liver extracts,[1-3] folic acid,[4-9] oral and parenteral vitamin B_{12},[10-18] a high-protein diet,[19] and penicillin.[20] In some anemias of pregnancy neither the morphological changes nor the response to treatment are sufficiently distinct to allow classification on a morphological or etiological basis.

An objective criterion for the classification of deficiency anemias would be the quantitative determination of the hematopoietic factors which may be lacking. In a preliminary study on 42 pregnant women suffering from a moderate anemia, low serum levels of vitamin B_{12} have been found.[21] In this study, therefore, serial determinations of iron and vitamin B_{12} concentrations in the sera of women during pregnancy and the puerperium were made. The results were then correlated with the morphological changes in the peripheral blood and bone marrow and with the hematological response to treatment.

Material and Methods

Hemoglobin determinations were performed on 2500 women during pregnancy and in the puerperium. Of these, 500 women were first examined in the antenatal clinic, and 2000 in the maternity ward following delivery. Hemoglobin values below 10.0 gm. per 100 ml. were considered as anemia.

Of the 500 women examined during pregnancy, 56 (11.2%) were found to be anemic. A group of 25 of these women was studied in detail. There were 4 primigravida, 7 had had two previous pregnancies, and 14 had had three or more previous pregnancies. Among the 2000 patients examined immediately following delivery, 220 (11%) were anemic. Of these, 75 women were studied in detail. None of these patients was a primipara, 10 had had one previous delivery, 24 had had three to six previous deliveries, and 30 had had more than six previous deliveries.

The majority of these women had immigrated to Israel from North Africa, Iraq, Iran, and the Yemen within the past five years. They were living in immigrant camps under depressed economic conditions, and their nutrition had been very poor. The daily caloric intake of these patients during the last trimester of pregnancy did not exceed 1000 Cal., and their total protein intake was less than 40 gm. per day. None of them showed signs of toxemia or gave a history of previous blood loss.

Most of the 100 patients studied in detail were examined at least three times during the observation period, although some could only be examined

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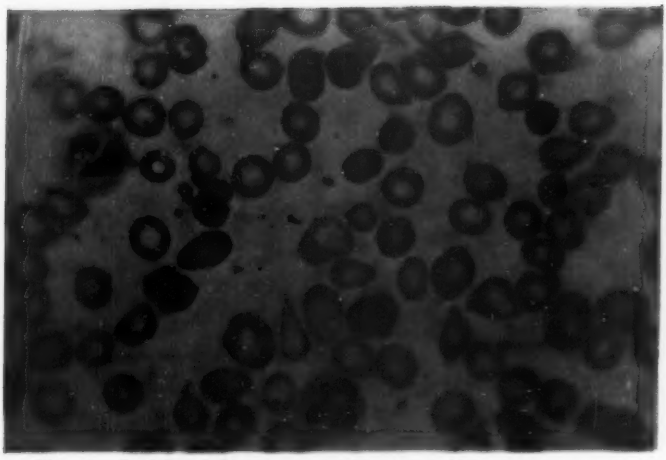

Fig. 1.—Peripheral blood smear showing anisocytosis, macrocytes, normocytes, and microcytes, with hypochromia, polychromatophylia, and slight poikilocytosis; enlarged approximately $2\frac{2}{3}$ times from mag. × 950.

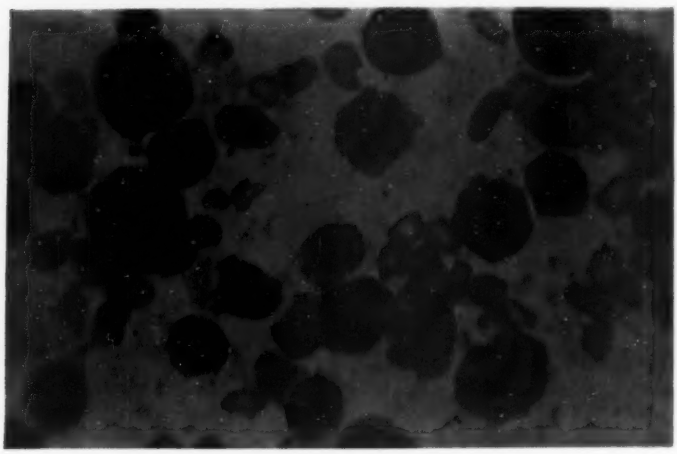

Fig. 8.—Photomicrograph of the bone marrow smear from a patient with dimorphic anemia with marked erythroid hyperplasia. Very young as well as later red cell precursors seen in the same slide; enlarged approximately $2\frac{2}{3}$ times from mag. × 950.

twice. Following delivery, 23 of the severely anemic patients were transferred to the medical ward for observation and treatment.

The following hematological studies were carried out: hemoglobin (acid hematin), red cell count, hematocrit, reticulocyte count, Price-Jones curve (in 22 representative cases), white cell count, and differential count. The serum iron level[22] was determined in 77 patients. Determination of vitamin B_{12} in the serum was done in all patients by microbiological assay using a mutant strain of Escherichia coli as the test organism. The normal range of serum vitamin B_{12} was found to be from 200 to 500$\mu\gamma$ per milliter.[23] Bone marrow smears from sternal aspiration biopsy, gastric juice analysis, and serum protein determinations were made in 20 patients, and in 10 of them paper electrophoresis of the serum was carried out.

Results

Clinical Symptoms and Signs.—All the patients complained of fatigue, palpitation, and dyspnea on exertion. Anorexia of a moderate to severe degree was a frequent symptom, but only a few patients had vomited during the first trimester of pregnancy. The physical examination revealed pallor of varying degrees and cheilosis in most of these patients. Flattening of the papillae of the tongue was found in a few instances only. There was no plato- or koilonychia. In about half of these patients a moderate to marked increase in the size of the liver and spleen was found.

In the 25 patients found to be anemic during the last trimester of pregnancy, the initial hemoglobin values ranged from 5.6 to 10.0 gm. per 100 ml. In some of these patients, the hemoglobin values were higher than 10.0 gm. per 100 ml. during the second trimester but gradually decreased during the subsequent months.

In eight of these patients there was an iron-deficiency anemia with low MCHC (below 28%), MCH (below 26$\mu\gamma$), and low serum iron concentration (from 18 to 62γ per 100 ml.). The vitamin B_{12} concentration in the serum of these patients was low normal (from 170 to 220$\mu\gamma$ per ml.). The red cells showed marked hypochromia and anisocytosis. In four other patients there was a macrocytic anemia with high MCV (above 92 cu.μ), high serum iron concentration (above 85γ per 100 ml.) and low serum vitamin B_{12} (from 50 to 120$\mu\gamma$ per ml.). Their peripheral blood smear showed macrocytosis with slight poikilocytosis.

The blood smears in most of the 13 remaining patients showed macrocytes as well as hypochromic normocytes and microcytes (dimorphic anemia [Fig. 1]). In most of these patients both serum iron and vitamin B_{12} concentrations were low (18-95γ per 100 ml., and 60-140$\mu\gamma$ per millimeter, respectively).

The hemoglobin values did not show significant changes during the course of the last trimester of pregnancy, but in the first three weeks following delivery there was a definite rise in both hemoglobin concentration and red blood cell count in all patients.

The serum iron levels showed a tendency to decrease as pregnancy progressed, reaching the lowest levels at the time of delivery.

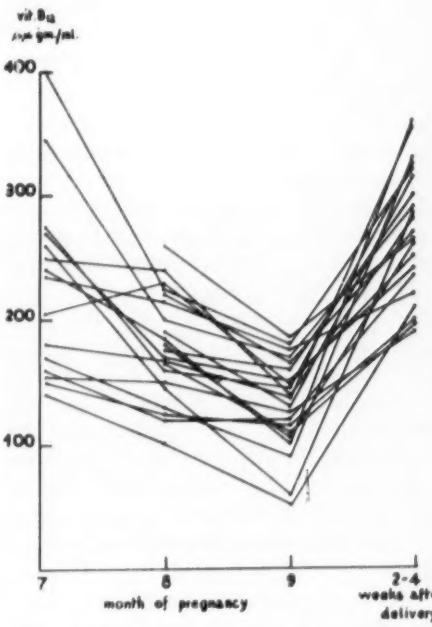

Fig. 2.—Serial serum vitamin B_{12} determination during the third trimester of pregnancy and two to four weeks following delivery. Serum vitamin B_{12} levels decrease as pregnancy progresses, then rise sharply in all cases after delivery.

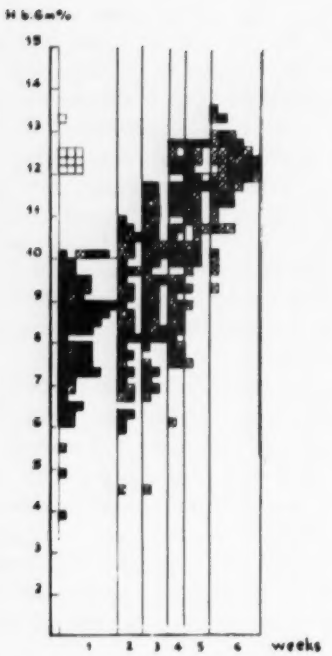

Fig. 3A.—Gradual increase in hemoglobin in 75 patients following delivery. Unfilled boxes: hemoglobin values in nonanemic women following delivery. Boxes with crosses: patients who received ferrous sulfate. Black boxes: patients recovering spontaneously.

The serum iron levels rose spontaneously in most of the cases after the delivery.

Repeated vitamin B_{12} determinations during pregnancy and in the postpartum period revealed a fairly constant pattern illustrated in 20 representative cases in Figure 2. The initial values of serum vitamin B_{12} were within the normal or low normal range, and there was a gradual decrease in most cases as pregnancy progressed. This decrease did not parallel the decrease in hemoglobin. In all cases there was a marked increase in the serum vitamin B_{12} concentrations two to four weeks following delivery, accompanied by a rise in hemoglobin values and red cell counts.

In 10 pregnant women with no anemia (in whom the red cell count ranged from 4,100,000 to 4,700,000 per cubic millimeter) and the hemoglobin values ranged from 12.0 to 13.1 gm. per 100 ml.), the serum vitamin B_{12} and iron concentrations were normal (295-350$\mu\gamma$ per millimeter and 92-170γ per 100 ml., respectively).

Of the 75 patients first seen after delivery, there were 22 with hypochromic iron-deficiency anemia, 7 with macrocytic hyperchromic anemia, and 46 with dimorphic anemia.

Hemoglobin values immediately after delivery in 43 patients ranged from 8 to 10.0 gm. per 100 ml.; in 29, from 6 to 8 gm. per 100 ml., and in three patients the hemoglobin was below 6.0 gm. per 100 ml. In 29 cases, where the spontaneous increase in the hemoglobin was slow during the first three weeks following delivery, the addition of iron markedly enhanced hemoglobin production. In 46 patients no treatment was required, and an increase of up to 5.0 gm. per 100 ml. of hemoglobin was seen within a six-week period after delivery; the lower the initial hemoglobin concentrations, the more rapid was the increase in hemoglobin. The hemoglobin values and red cell counts reached normal levels by the end of the sixth week post partum (Figs. 3 and 4). Together with this improvement the hypochromia and anisocytosis disappeared.

The serum iron of 52 patients after delivery was below 50γ per 100 ml. in 24 patients, between 50 and 85γ per 100 ml. in 19 patients, and over 85γ per 100 ml. in 9 patients. An increase in serum iron of varying degree was observed also in patients who were not given iron (Fig. 5).

The serum vitamin B_{12} concentration gradually increased in all these patients following delivery, reaching low normal or normal values (145-700$\mu\gamma$ per millimeter) by the end of the sixth week (Fig. 6).

The dimorphism seen in the smears of the majority of these patients was studied by means of Price-Jones curves in 22 representative cases. A marked spread to both sides was found at the beginning of the observation period. As the anemia improved, the curves became normal (Fig. 7).

In three patients with hypochromic iron deficiency anemia the bone marrow was

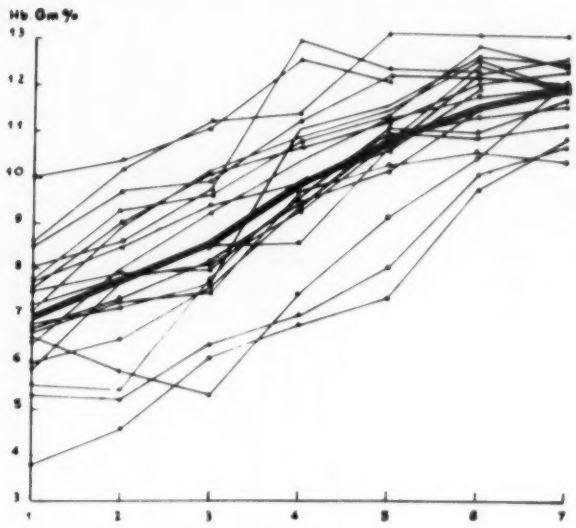

Fig. 3B.—Gradual elevation of hemoglobin following delivery in 20 anemic patients. Thick line represents mean increase in hemoglobin.

highly cellular. The erythroid series was erythronormoblastic. There were no typical megaloblasts, and young atypical megaloblasts were rarely encountered. There was marked proliferation of the myeloid series, but no atypical or giant myeloid cells were seen. The bone marrow of five patients with macrocytic hyperchromic anemia was highly cellular. Typical megaloblasts ranged from 2% to 14%, proerythroblasts from 5% to 17%, and up to 23% of macronormoblasts were found. In the myeloid series giant metamyelocytes as well as giant band forms were frequently seen. There was hypersegmentation of the nuclei of the polymorphonuclear granulocytes. In 12 patients suffering from both iron and vitamin B_{12} deficiencies the bone marrow was hypercellular. Occasional megaloblasts were seen, but they never exceeded 3%; proerythroblasts were present as well, reaching a maximum of 12% of the total count. The late erythroblasts and normoblasts made up the bulk of the erythroid cells. In the myeloid series giant myeloid forms were seen, and a few polymorphonuclear granulocytes showed hypersegmented nuclei (Fig. 8).

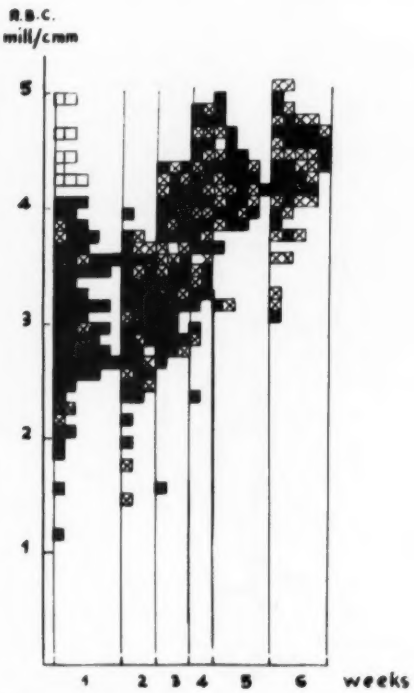

Fig. 4A.—Gradual increase in the red cell count in 75 anemic patients following delivery. Legend same as in Figure 3A.

The serum protein levels determined in 20 patients ranged from 5.5 to 7.1 gm. per 100 ml. The albumin ranged from 3.3 to 3.8 gm. per 100 ml. and the globulin from 2.2 to 3.3 gm. per 100 ml. The serum elec-

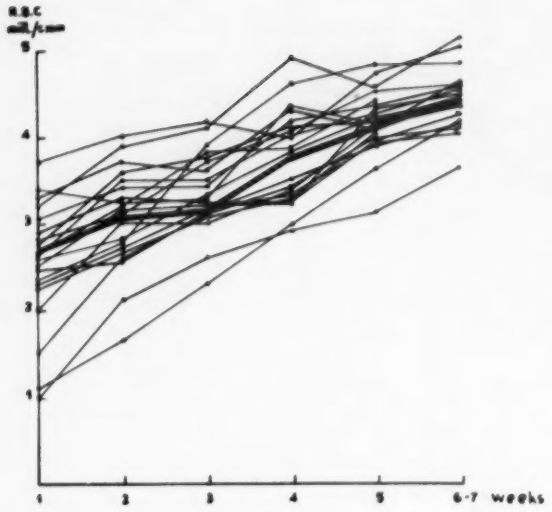

Fig. 4B.—Gradual elevation in the red cell count in 20 anemic patients following delivery. Thick line represents the mean values.

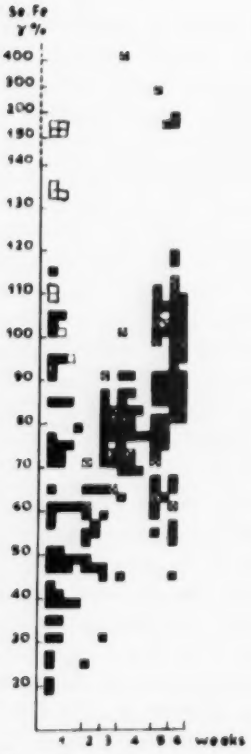

Fig. 5.—Gradual increase in serum iron levels in 52 anemic patients following delivery. Legend same as for Figure 3A.

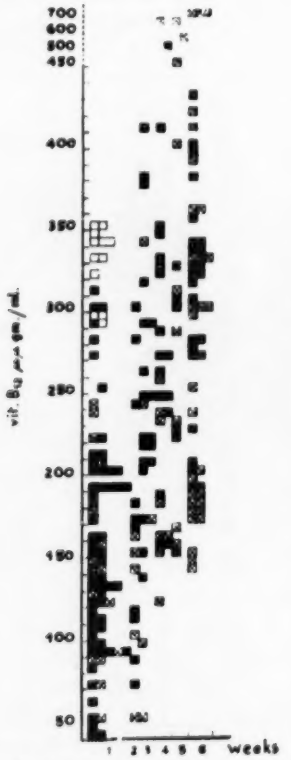

Fig. 6.—Gradual increase in serum vitamin B_{12} levels in 75 patients following delivery. Legend same as for Figure 3A.

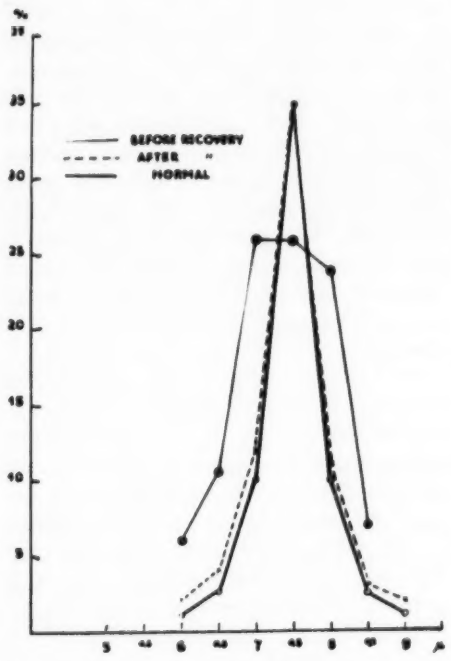

Fig. 7.—Price-Jones curves showing spread in both directions at the beginning of the observation period. Returned to normal four weeks later, together with the hematological improvement.

trophoretic patterns in 10 of these cases were normal.

In 10 women examined post partum with normal hemoglobin (12.0-13.0 gm. per 100 ml.) and normal red blood cell counts (4,100,000 to 4,700,000 per cubic millimeter) the serum iron and vitamin B_{12} levels were also normal (90-180γ per 100 ml., 260-370$\mu\gamma$ per millimeter, respectively).

Comment

In 30 of the 100 patients followed during pregnancy and puerperium there was an iron-deficiency anemia manifested by hypochromia, low serum iron, and low MCHC. In 11 patients the anemia could be classified as hyperchromic macrocytic with high MCV and normal or high serum iron. In this last group the serum vitamin B_{12} concentration was low as in pernicious anemia in relapse. The anemia found in these women is usually called megaloblastic anemia of pregnancy. In our cases the term "megaloblastic anemia" is not justified because of the small percentage of typical megaloblasts found in the bone marrow. The bone marrow showed marked erythroid hyperplasia with a prevalence of early red cell precursors, the morphology of which was not uniform. Some of them resembled typical megaloblasts, while others were either early erythroblasts or transitional cells. These cell types are differentiated from each other with considerable difficulty.[24,25]

In the majority of our cases (59%), however, both macrocytes as well as microcytes and normocytes were seen in the same slide, but most of these cells were hypochromic. This wide variation in the morphology of erythrocytes was reflected in the spreading of the Price-Jones curves in both directions. In these cases the serum iron as well as the serum vitamin B_{12} levels were either low or low normal, indicating a combined deficiency.

In 10 women without anemia examined once during the last trimester of pregnancy the serum vitamin B_{12} level was above 200$\mu\gamma$ per millimeter. In most of our anemic patients there was a gradual fall during the last trimester below 200$\mu\gamma$ per milliliter, followed by a rise during the two to four weeks after delivery. The rise of serum vitamin B_{12} after delivery was accompanied by an increase in hemoglobin and red cell values. Low vitamin B_{12} concentrations during pregnancy were previously reported by us[21] and were also observed in Germany in 20% of pregnant women.[26]

At variance with our findings and those reported by Heinrich,[26] Mollin and Ross[27] found normal serum vitamin B_{12} values in 29 of 31 cases, and Girdwood[28] in 15 cases of megaloblastic anemia of pregnancy. These latter authors, however, report only single determinations of serum vitamin B_{12} at some point during pregnancy and the puerperium. Our studies indicate the importance of serial examinations in showing

the changes of serum vitamin B_{12} levels throughout this period.

It has been generally accepted that megaloblastic anemia of pregnancy responds readily to crude liver extract and folic acid, but not to vitamin B_{12}.[1-3,5-9,29] Recent reports from tropical countries, however,[10-14,16,30] and nontropical countries[15,17,18] record favorable therapeutic effects of vitamin B_{12} in some cases of megaloblastic anemia of pregnancy.

As various agents may be effective in the treatment of macrocytic anemia of pregnancy, this anemia may be due to deficiency of several factors, among them vitamin B_{12}. In different cases these factors may operate either separately or in combination. Furthermore, it is possible that some cases of "megaloblastic anemia of pregnancy" may not be primarily deficiency disease. A remarkable example of the development of megaloblastic anemia not due to lack of intrinsic or extrinsic factors is the causation of megaloblastic anemia by anticonvulsive agents.[31-33]

While vitamin B_{12} deficiency was present in 70% of our patients, only 11% had a hyperchromic macrocytic anemia. Concomitant iron deficiency might have prevented the development of the typical morphological picture of macrocytic anemia in the remaining 59% of patients. In these cases macrocytosis was commonly associated with hypochromia. This type of anemia is usually called dimorphic anemia.[34,35] The bone marrow was characterized by excessive erythronormoblastic hyperplasia and by the presence of giant stab cells and giant myelocytes. Typical megaloblasts were found only in a few cases and then in only a small percentage. A high incidence of dimorphic anemia in the general population as well as in pregnant women was found in India by Das Gupta and Chatterjea.[8,13]

It is important to note that deficiency of vitamin B_{12} may be present without morphological manifestations in the peripheral blood and bone marrow. Thus low vitamin B_{12} levels were found in cases of pernicious anemia in remission with inadequate treatment.[36] Furthermore, vitamin B_{12} depletion may precede the appearance of macrocytic anemia by a long period in cases of total gastrectomy[37,38] as well as in "vegans"[39,40] living on a strictly vegetarian diet with total exclusion of animal protein. While in vegans and after subtotal and total gastrectomy vitamin B_{12} deficiency and macrocytic anemia develop over the course of several years,[37-40] in pregnancy vitamin B_{12} depletion and anemia appear within a few months.

The cause of vitamin B_{12} deficiency in pregnancy must be sought first in the increased demand due to the utilization of large amounts of vitamin B_{12} in the growth of the embryo and for its blood cell production. In the face of this increased demand of vitamin B_{12} the diet of our patients during pregnancy as well as during preceding years of child-bearing was notably poor in animal protein. The daily intake of all proteins averaged 40 gm., which is far below the 80 gm. required in the latter half of pregnancy.[41] The importance of protein depletion as an etiologic factor in the macrocytic anemia of pregnancy is well recognized.[42,43,48]

There was no reason to assume a disturbance in vitamin B_{12} resorption in our patients. None of them suffered from vomiting or diarrhea during the latter half of pregnancy. In 20 severely anemic women the gastric juice analysis showed the presence of free hydrochloric acid without stimulation. Although we did not test for the presence of intrinsic factor in our patients, Badenoch et al.[9] showed that the absorption of labelled vitamin B_{12} was normal in a group of nine women with megaloblastic anemia of pregnancy. Heinrich[26] found that oral administration of vitamin B_{12} to pregnant women with low serum vitamin B_{12} concentrations was followed by increased excretion of vitamin B_{12} in the urine as in normal persons, thus suggesting the presence of intrinsic factor in the stomach of these women.

The available evidence supports the contention that inadequate supply and increased requirements of vitamin B_{12} are the causative factors in the development of vitamin B_{12} deficiency in pregnancy. The same disproportion between supply and demand occurs also in the case of iron, producing the frequent association of both of these deficiencies in our patients. The frequency of this combined deficiency (59% of our anemic women) may be explained by a combination of circumstances consisting of malnutrition, frequent pregnancies, and perhaps climatic conditions.

The blood loss during delivery did not play a significant role in the cases of anemia detected after delivery. This blood loss was estimated to be from 200 to 500 ml. However, in spite of this moderate blood loss, four patients developed shock at delivery, necessitating blood transfusion.

The blood regeneration following delivery was rapid in most of these patients, particularly in those who were transferred to the medical ward and were given a high-caloric, high-protein, vitamin-rich diet. The rapid hematological improvement which followed provides additional evidence for the importance of both malnutrition and the increased demand during pregnancy for vitamin B_{12} and iron in the causation of anemia. Hemoglobin production in the postpartum period was especially marked in untreated cases with extremely low hemoglobin values at the time of delivery. The hemoglobin concentration often doubled or trebled within four weeks while in hospital. This observation suggests that the absorption and utilization of dietary iron must have been very high and may have been facilitated by a high intake of citrus fruit, which is richly provided for in our patients' diet.[44] In some cases, however, the spontaneous hemoglobin production was limited, and values after a moderate increase remained unchanged. On treatment with oral iron there was a further increase in the hemoglobin concentration in these cases, unless interfering factors such as infection were present.

It is obvious that these marked changes in the hematological findings and serum vitamin B_{12} following delivery could not be ascribed solely to alterations in blood volume alone which occur during the latter half of pregnancy and in the postpartum period.[14, 45, 46]

Summary

Of a total of 2500 women examined during pregnancy and in the puerperium, 276 (11%) were found to be anemic (hemoglobin below 10.0 gm. per 100 ml.).

Hematological examinations and serum iron and vitamin B_{12} determinations were made repeatedly in 100 of these anemic women during the last trimester of pregnancy and in the postpartum period. Thirty of them had hypochromic iron-deficiency anemia with low serum iron and normal serum vitamin B_{12}, eleven patients had hyperchromic macrocytic anemia with very low serum vitamin B_{12} and normal or high serum iron concentrations. Fifty-nine patients showed the morphological features of dimorphic anemia with both low serum vitamin B_{12} and low serum iron values.

Spontaneous hematological improvement was observed in most patients in the postpartum period together with a gradual increase in serum vitamin B_{12} and iron concentrations.

Malnutrition, increased requirements during pregnancy, and frequent pregnancies are considered to be responsible for the iron and vitamin B_{12} deficiencies.

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The Identification and Clinical Significance of Casts

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In many cases of congestion, and in inflammation of the kidney, a spontaneously coagulable material is effused into the tubes and coagulates there forming a cast or mould of the tube . . . entangles in its meshes any structures which may be there at the time. The characters of the cast will vary . . . according to the state of the tubes. By observing . . . we are often able to form a correct notion concerning the nature of morbid changes going on in tubes at the time the cast was formed. It has been stated that the different morbid states of the kidney are but different stages of one and the same disease . . . a few months' careful study in the wards of a hospital and in the dead-house, will serve to convince any unprejudiced person that the nature of renal disease may be diagnosed in many cases by the microscopical characters of the urinary deposit, and that there are several essentially distinct forms of renal disease.

These words of Beale, published in 1870,[1] serve as a pertinent introduction to an ancient topic here considered in our modern time. Uroscopy was probably the first known clinical laboratory determination and remains today as the most frequently indicated laboratory test and the one with the highest practical yield in the physician's office.

It is our intention to denounce abandonment of microscopy even in this atomic age. No more potent argument could be mustered than a consideration of casts in the urine, for a cast, with its measurable dimensions of size, form, composition, and incidence, is a readable message from the nephron which formed it.

It is the plan of this paper to outline simple methods for examination of casts; to formulate a clear, easily remembered classification; to teach identification of casts in the only effective way, by direct photographs, and to make some clinical correlations.

Methods of Examination

General Considerations.—A fresh, clean-catch specimen collected after dehydration or in the morning after cleansing the urethral orifice offers a satisfactory medium for observing casts. Vaginal, rectal, and fecal contamination from the bed pan are to be avoided. Hyaline casts dissolve in neutral saline[2] more dilute than 0.5% (S. G. 1.003) or in an alkaline solution. As the pH rises, more solute is required to maintain the form of casts. Thus, a concentrated, acidic urine is ideal. Contrary conditions may result in dissolution of casts in the bladder or while urine is left standing in the laboratory. Where renal failure or a specific disease process (e. g., renal hyperchloremic acidosis[3] with inability to acidify urine) prevent concentration and/or acidification in bladder urine, the use of NaCl crystals or a few drops of concentrated HCl may prevent cast dissolution. A standardized centrifuge technique should be used, such as 15

Fig. 1A.—Fatty cast under reduced light; reduced approximately 2/5 from mag. × 860.

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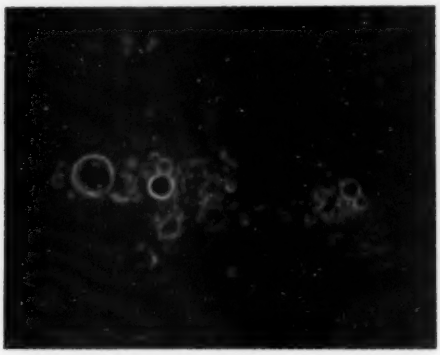


Fig. 1B.—The same fatty cast seen with phase contrast microscopy; reduced approximately 2/5 from mag. ×860.

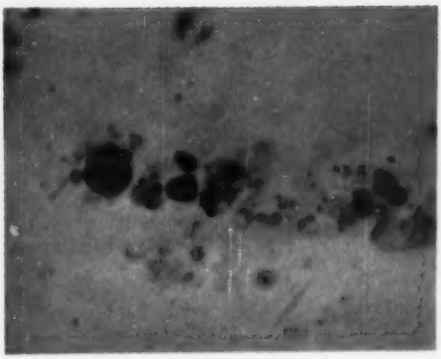


Fig. 1C.—The same fatty cast after staining with Sudan III; reduced approximately 2/5 from mag. ×860.

ml. of morning urine in conical tube at 3000 rpm for five minutes, or preferably the use of a one-fifth-hour volume as described by Lippman.[4] The supernatant is withdrawn or discarded to 0.5 ml. and the sediment reconstituted by finger flicking. Casts are usually found near the edge of a cover slip and can be made to roll by depressing one corner with a pencil point.

Procedures.—1. Examination Under Reduced Light Through a 10× or Low-Power Objective: By proper use of an Abbe condenser with diaphragm, casts can be well outlined and counted. A 20× objective with 10× ocular will bring most casts to full field. High-power objective will be needed to identify morphology of inclusions. A simple qualitative grading of the incidence of casts may be made as follows: 0 or occasional, 1 cast/20 h. p. f.; 1+ or few, 2-3 casts/20 h. p. f.; 2+ or moderate, 5-10 casts/20 h. p. f.; 3+ or many, 1 cast/h. p. f.; 4+ or loaded, more than 1 cast/h. p. f.

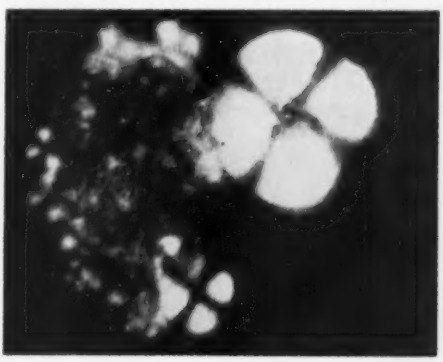
2. Phase-Contrast Microscopy: With the addition of a special condenser and objectives, a standard microscope may be converted to phase contrast. Some manufacturers offer a range of light, medium, and dark contrast. This device artificially retards diffracted light part of a wave length and markedly improves the visibility of objects with a refractive index close to that of their liquid medium. Since glass, urine, and hyaline matrix have similar refractive indices, the technique is valuable for outlining plain hyaline casts as well as their filaments, cell membranes, nuclei, bacteria, and inclusion bodies. Both bacteria and cytoplasmic granules can be well differentiated. Slight movement of a properly focused condenser can produce light abberation, and it is possible by this technique to introduce a pleasing blue color into unstained sediments. The technique is illustrated in Figure 1, which shows the same hyaline cast with fatty inclusions as viewed with ordinary reduced light (Fig. 1*A*), phase contrast with aberration (Fig. 1*B*), and with an apochromatic optical system after staining the cast with Sudan III (Fig. 1C).

3. Polarized Light[5]: Doubly refractile fat bodies, either free (Fig. 2), in renal epithelial cells, or in casts, are best observed under polarized light, which may be obtained by use of Nicol prisms, polarizing films in ocular and condenser (obtained from the American Optical Co. or home-made from 3-D glasses).

4. Strong Iodine (Lugol's) Solution (Iodine 1.0 gm., KI 2.0 gm., H_2O 300 ml.): This will tinge casts satisfactorily if one drop is added to sediment tube or slide. Epithelial cells will appear light yellow. WBC will be dark yellow to mahogany. Granules will be dark.

5. Glitter-Cell Stain: Solution A is made up of methylrosaniline chloride (crystal violet), 3.0 gm.;

Fig. 2.—Doubly refractile fat body (cholesterol esters) from the urine of a woman with the nephrotic syndrome and proven Kimmelstiel-Wilson's disease. Note the typical "maltese cross" appearance of the large fat body and its satellites (polarized light).



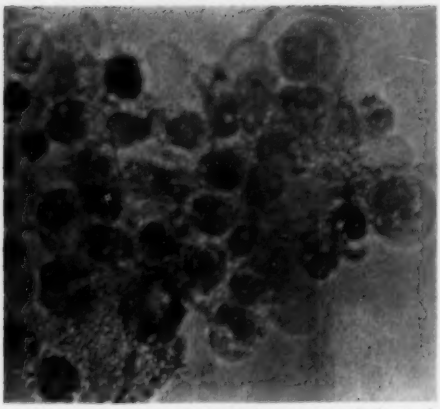


Fig. 3.—A clump of leukocytes and bacteria from the urine of a patient with chronic pyelonephritis. The large pale-staining cells on the periphery were typical "glitter" cells; Sternheimer-Malbin; reduced 1/3 from mag. × 860.

95% ethyl alcohol, 20.0 ml., ammonium oxalate, 0.8 gm., and purified water to 80 ml. Solution B is made from safranine O, 0.25 gm.; 95% ethyl alcohol, 10.0 ml., and purified water to 100 ml. Mix 3 parts A and 97 parts of B and filter. This is kept in a dropper bottle. For staining, put 1 drop of the stain in the reconstituted sediment in the centrifuge tube. Examine under cover slip.

Sternheimer and Malbin[6] described this supravital stain for leukocytes with special staining characteristics (Fig. 3). We have had extensive experience with the stain over the past five years and find it extremely useful for teaching purposes in the differentiation and identification of formed elements.[7] Hyaline casts stain pink to purple (Fig. 4); epithelial casts are dark purple; red cells, faint lavender; polymorphoneuclear leukocyte nuclei, orange-purple (normal) or light blue to colorless (glitter cells). Bladder epithelial nuclei stain blue, and vaginal epithelial nuclei purple. Trichomonads are light blue. This stain was used in the sediments photographed in Figures 3, 4, 5, 8, 10, and 12.

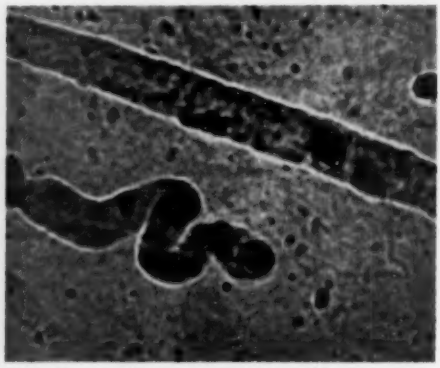


Fig. 4.—Straight and curled hyaline casts with leukocyte and granular inclusions. One of the included white cells had the staining characteristics of the "glitter" cell. The urine is from a patient with chronic pyelonephritis; Sternheimer-Malbin stain; reduced approximately 2/5 from mag. × 300.

6. Negative Staining: Brewer[8] has used negative, or silhouette, staining for hyaline casts and epithelial cells. Mix 1 drop of India ink (Mandarin black, Winsor and Newton) with 1 drop of urinary sediment on the glass slide.

7. Staining for Erythrocytes and Granular Casts[9]: Stock solutions (brown bottle)—1%

Fig. 5.—A collection of casts from the first urine passed after 45 days of anuria by a 6-year-old boy with nephrotic syndrome and chronic glomerulonephritis. In the center is a fresh, dense hyaline cast. Below is a degenerating, fragmented cast. Above is shown the sharp contrast between a broad and narrow hyaline cast. In the upper center is a hyaline cast with inclusions that stain like the red cells which are floating in the surrounding urine; Sternheimer-Malbin; reduced approximately 2/5 from mag. × 100.

Fig. 6.—In the center is a dense hyaline cast with one red cell and two discrete inclusions. Above is a short hyaline cast with granular particles. The urine is from a patient with chronic glomerulonephritis; contrast stain; reduced approximately 2/5 from mag. × 215.

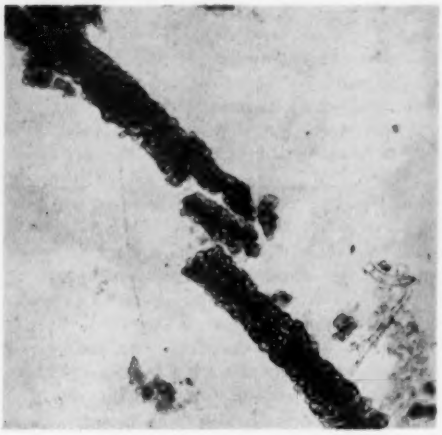


Fig. 7.—Hyaline blood cast from the urine of a 5-year-old boy with acute hemorrhagic glomerulonephritis. Note the densely packed erythrocytes and dark strands; unstained; reduced approximately 3/10 from mag. × 150.

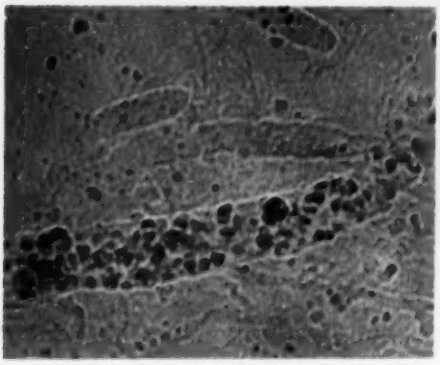
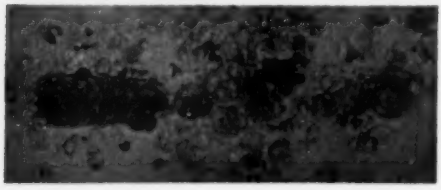


Fig. 8.—Hyaline casts, plain and with white cell inclusions; Sternheimer-Malbin stain; reduced approximately 2/5 from mag. × 300.

Fig. 9.—Hyaline cast with tubular epithelial cell inclusions from the urine of a 9-year-old boy with acute glomerulonephritis (Case 1). The hyaline matrix is clearly seen between district epithelial cells on the right. The cells have degenerated to form a coarsely granular segment on the left; contrast stain; reduced approximately 2/5 from mag. × 860.



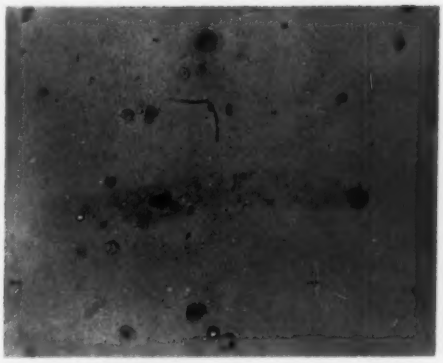


Fig. 10.—Hyaline cast with single renal epithelial cell in tip and adherent bacteria; Sternheimer-Malbin stain; reduced approximately 2/5 from mag. × 645.

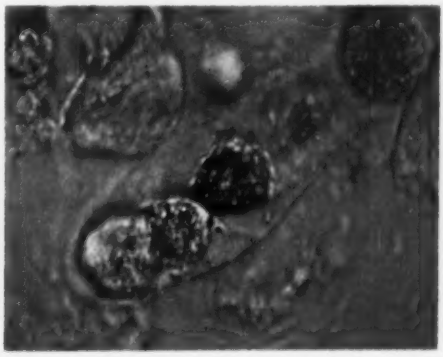


Fig. 11.—Hyaline case with epithelial cell inclusions showing fatty degeneration. The urine is from a 24-year-old woman with nephrotic syndrome; unstained; reduced approximately 2/5 from mag. × 860.

Fig. 12.—Broad, desquamated epithelial cast from the urine of a 9-year-old boy in convalescent phase of acute glomerulonephritis (Case 1); Sternheimer-Malbin stain; reduced approximately 2/5 from mag. × 430.

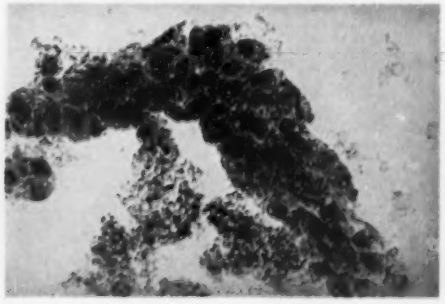


Fig. 13.—Fresh epithelial cell cast from the urine of a 9-year-old boy emerging from the oliguric phase of acute glomerulonephritis. The tubular epithelial cells in the central convoluted portion of the cast show round form and distinct cell outline. They merge into coarsely granular material in the dilated ends. The size of an attached red cell may be compared; light methyl blue; reduced ⅓ from mag. × 860.

aqueous benzidine HCl; 2% aqueous sodium nitroprusside; 30% hydrogen peroxide. Working solutions—Solution A: 0.1% benzidine in 0.2% nitroprusside; Solution B: 3.0% hydrogen peroxide. Add 1 drop of sediment to 1 drop of Solution A. Mix thoroughly and add 1 drop of Solution B. In 2-5 minutes red blood cells in casts are well stained deep blue or purple fading to light blue on deterioration. Granules in granular casts have the deep purple of erythrocytes. Hyaline matrix, fungi, spores, and yeasts do not stain. Leukocytes show pale gray cytoplasm and dark nucleus.

8. Contrast Stain for Casts[10]: Solution A: 0.5% eosin in water. Solution B: 1 ml. of 1% aqueous methyl blue added to 10 ml. of saturated picric acid and 10 drops of glycerin. To decanted centrifuge tube add 1 drop of Solution A, shake 1-2 minutes. Add 1 drop of Solution B. The mixture should be blue-green. Hyaline casts and cylindroids stain clear blue, granular material stains a darker blue. Renal epithelial cells stain red-orange or yellow. RBC's are brighter red. WBC's are red or blue. Fat is unstained. This stain was used for the photograph in Figures 6, 9, and 15.

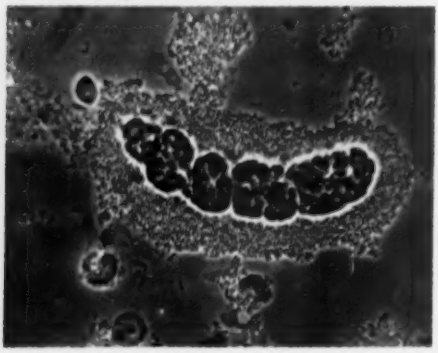
9. Preparation of Permanent Smears[11]: Spread reconstituted sediment over 20×40 mm. area on slide. Dry. Dip in 99% isopropyl alcohol 1 minute, dip in 90% isopropryl alcohol 15 seconds. Dip in Haines hemotoxylin to even coverage and leave 2 minutes. Drain. Rinse in tap water to clear. Dip in 2% aqueous eosin—45 to 60 seconds. Wash in tap water 15 seconds. Dip 90% isopropyl 15 to 20 seconds, 99% isopropyl alcohol to dehydration.

Fig. 15.—A waxy cast is seen in the upper right and a moderately broad, granular cast is on the left. Red and white blood cells float near by. The urine is from a 14-year-old boy recovering from severe acute glomerulonephritis; contrast stain; reduced approximately 2/5 from mag. × 645.

Clear in xylene and mount with cover slip in gum dammar or Clarite.

Fixed smears have all the advantages of a permanent record: they can be examined at leisure by the physician, they make it possible to compare patients or the same patient before and after treatment. They also permit photography with the usual professional camera, which is horizontal.

Fig. 14.—Epithelial cell cast surrounded by bacteria. The urine is from a patient with chronic glomerulonephritis, nephrotic syndrome, and pyelonephritis; phase-contrast; reduced approximately 2/5 from mag. × 430.



Classification of Casts

A. Hyaline (transudation) casts—plain (Fig. 5) or with

1. Red cell inclusions—hyaline matrix plus red blood cells (Fig. 6)

2. Hyaline-blood cast—dense red blood cells and fibrin (Fig. 7)

3. Polymorphonuclear leukocyte inclusions (Fig. 8)

(*a*) Purple- or orange-staining polymorphonuclear cells

(*b*) Glitter cell inclusions—blue leukocytes with granular cytoplasm

4. Tubular epithelial cell inclusions (Figs. 9, 10, 11)

5. Bacterial inclusions or adsorption of bacteria on cast surfaces (Fig. 10)

6. Crystal inclusions or adsorption, e. g., urates

7. Granular inclusions—degenerated cellular debris (Fig. 9)

8. Fatty inclusions or doubly refractile fat bodies (Figs. 1, 2, 11)

9. Bile-stained inclusions

10. Other

B. Epithelial cell (desquamation) casts—progressive stages

1. Fresh—cell margin distinct (Figs. 12, 13, 14)

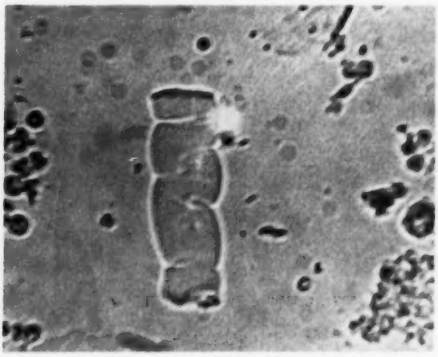


Fig. 16.—Waxy cast from the urine of a patient with chronic glomerulonephritis. Note the refractile margin and tendency to crack.

2. Coarsely granular—cells have lost integrity (Figs. 9, 13)

3. Finely granular—particles are smaller (Fig. 15)

4. Waxy—homogeneous, hard, refractile (Figs. 15, 16)

5. Fatty—fatty degeneration in cells

6. Tumor cells

7. Broad or renal failure cast—a granular cast from dilated nephrons (Fig. 17)

C. Mucus casts

D. Casts of unusual composition

1. Bence-Jones protein (Fig. 18)
2. "Amyloid"
3. Myoglobin
4. Hemoglobin
5. Dextran
6. Globin
7. Other

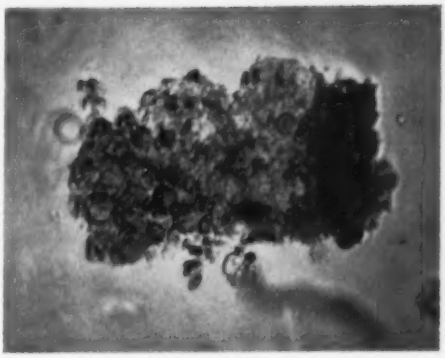


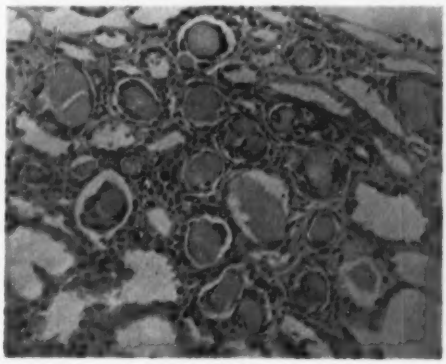
Fig. 17.—Broad granular cast with red cell inclusions from the urine of a patient in the recovery phase of severe acute glomerulonephritis; eosin stain; reduced approximately 2/5 from mag. × 860.

E. Pseudo cast

1. Agglutinated red cells
2. Agglutinated white cells
3. Packed urates (e. g., gout) or other crystals
4. Cells clinging to mucous thread
5. Bacteria clinging to mucous thread
6. Degenerated spermatozoa
7. "Fibrin" or mucous threads

The uroscopist who intends to interpret urinary sediments for clinical or research purposes must be meticulous in the identification of casts and must be able correctly to evaluate the microscopic appearance of pseudocasts as well as the other extraneous objects which may appear in the urine. Some examples of extraneous objects are

Fig. 18.—Highly eosinophilic casts in the dilated tubular lumina of a 34-year-old man with multiple myeloma and Bence-Jones proteinuria. Note the typical invasion of casts by hyperplastic, large epithelial cells. The section is from a renal biopsy; hematoxylin and eosin; reduced approximately 2/5 from mag. × 160.



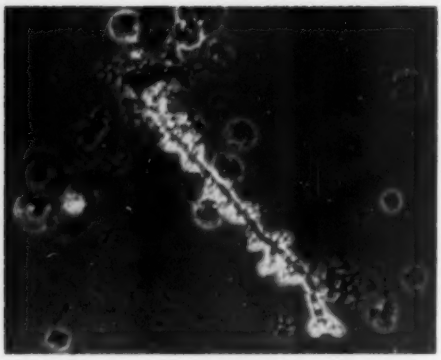


Fig. 19.—Hypha and spores of fungus in the urine of a patient with chronic glomerulonephritis. The small, dark objects are bacteria. To the left are spores within polymorphonuclear leukocytes; phase contrast; reduced approximately 2/5 from mag. ×400.

human, cat, dog, or blanket hair; wool, cotton, flax, and silk fibers, feathers; lubrication oil or jelly; hyphae and spores from saprophytic fungi (Fig. 19); vegetable fibers; mucous shreds and other material frequent in urine specimens from the hospital bed pan; starch, milk, tea leaves, bread crumbs, and other debris which may be shaken from sheets or dropped from a tray into a bedside urinal.

Interpretation of Casts

There is no question that casts are often found in the properly examined urine of office and hospital patients. One author reports a 60% incidence in 310 consecutive office patients.[12] The crucial questions are the following: (*a*) Can identification of casts be valuable as a screening test or case-finding mechanism in the discovery of masked or asymptomatic renal disease? (*b*) Are casts of specific diagnostic value? (*c*) Do they permit any helpful correlations with renal physiology or pathology? (*d*) Do they aid the clinician in treatment or prognosis?

Our purpose is to indicate reasons for an affirmative answer to these questions and therefore to claim that urinary microscopy is a valuable laboratory test which can and should remain in the physician's hands. It is so basically a part of the complete examination that it should never be delegated to a casually trained technician or to a commercial laboratory.

Hyaline casts are the gel of proteins which have presumably traversed the capillary membrane. Such gel formation is apparently dependent on concentration of protein, acidification, concentration of other solutes, and possibly the presence of other substances, such as mucoprotein or chondroitin-sulfuric acid.[13] Figure 20 shows periodic-acid-Schiff-positive material resembling a fine cast in the lumen of a medullary tubule. Any formed element present at time of gel formation will be entrapped. This makes the hyaline cast a slate on which we read the events which have transpired up in the nephron and forms the basis of our subclassification under A. Hyaline casts are of varying widths, may be straight, folded, serpentine, or have wavy "tails." Narrow tapered casts with tails have been called cylindroids, a classification devoid of meaning. There is some relationship between cast width and nephron size, the casts of children appearing much narrower, in general. When any significant percentage of hyaline casts are broad (Fig. 5), one may infer loss of nephrons or obstruction with subsequent dilatation. Such casts are common in those renal diseases which

Fig. 20.—PAS-positive protein cast in the medulla of a patient with acute renal insufficiency due to sulfonamide crystallization; hematoxylin and eosin; reduced approximately 2/5 from mag. ×400.

produce fibrosis of glomeruli, atrophy of nephrons, and steps leading to the development of a "thyroid kidney." Hyaline casts may be seen in apparently normal urine, but in relatively small numbers. They may be seen in any except the first two causes of proteinuria, as they are classified in Table 1.

TABLE 1.—*Classification of Proteinuria*

1. Pseudoproteinuria
(*a*) Iodides used in roentgenography
(*b*) Excess urates
(*c*) Spurious—added to urine (egg, serum, etc.)
2. Urologic
3. Psychosomatic ("emotional," "stress," "autonomic")
4. Febrile
5. Transient ("benign," "intermittent," "muscular," "exercise," "march," "physiological," "idiopathic")
6. Postural ("orthostatic," "lordotic," "constitutional")
7. Prerenal
8. Renal

The number of casts, chiefly hyaline, has been noted to increase strikingly after exercise, particularly of the strenous variety. They increase with the number of rounds boxed, the number of miles run, the minutes of football played, etc. Roberts [14] made 41 observations in 31 subjects after football and handball and found the cast excretion to vary as follows in thousands of casts/hour: before exercise, 2.09±0.09; during exercise, 37.94±11.16; after exercise, 10.00±3.83. Behrman [15] studied 20 runners in the Boston Marathon. Before the race 20 of 20 had negative protein and sediments, except for 7 with a rare hyaline cast. After the race all had albuminuria and a marked increase in casts. Thirteen had more than 25 casts/l. p. f., and one had 450 casts/l. p. f. Such findings may be brushed aside as "nonpathologic." However, the correlations which exist with the degree and duration of exercise permits the converse interpretation that focal ischemia of the capillary tuft may occur along with dehydration and metabolic acidosis. We have recently seen a healthy young man who took 6 gm. of sulfadiazine and became anuric with crystallization on the day following strenous swimming and diving.

Hyaline and granular casts are increased in congestive failure, as noted by Stewart,[16] but we have found no correlation with the clinical estimate of the degree of failure. We have seen casts and albuminuria appear after injection of mercurial diuretic, and casts may be markedly increased in patients in congestive failure who are given ammonium chloride or cation exchange resins; Friedman [17] has reported up to 30-40 casts/l. p. f. with an ammoniated sulfonic exchange resin. Sporadic simple hyaline casts are thus a normal finding. Increased casts may be concomitant with proteinuria, which requires investigation as to type and cause. Marked increase in hyaline casts may occur with strenous exercise, procedures resulting in acidification, and either congestion or ischemia in the kidney. Life insurance statistics [10] covering 52,436 study years suggest that the finding of casts at rest may herald the onset of cardiovascular or renal disease 10 years in advance. For 10 years following the demonstration of casts, death rates remained normal and then rose to 63% above the control rate.

With the identification of inclusions, hyaline casts become interesting for the messages they bear. Red cells in a cast mean renal hematuria and should always be considered pathologic. They may be the only manifestations of acute glomerulonephritis, SBE (subacute bacterial endocarditis) kidney, renal infarction, or collagen kidney. When the red cells increase in number, the cast takes on an orange-yellow appearance. "True" blood casts are homogeneous without distinguishable cell margins and may represent red cells in a fibrin clot. Addis considered the blood cast pathognomonic of acute glomerulitis. Figure 21 illustrates three stages in the formation of a blood cast: In *A*, red cells are free in the lumen; in *B*, they are in a protein matrix and are degenerating; in *C*, they have blended into a homogeneous blood cast.

Leukocytes in casts are thus labelled as renal in origin. They may be seen in acute glomerulonephritis and nephrotic syndrome, but more often signal infection. Tissue proven pyelonephritis can exist both clinically and experimentally with absent or

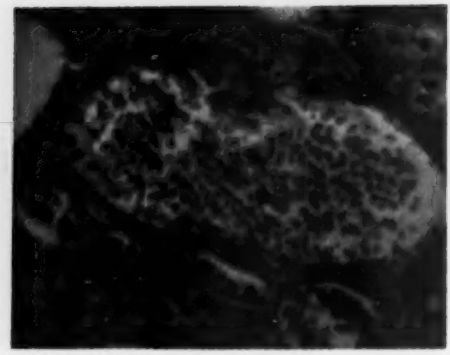
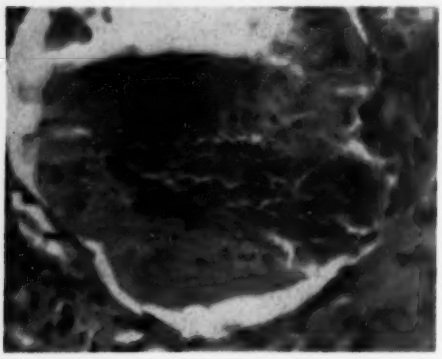


Fig. 21A.—First stage in the development of a blood cast. Red cells are seen free in a dilated lumen in a patient with acute renal insufficiency due to sulfonamide crystallization; hematoxylin and eosin; reduced approximately 2/5 from mag. × 400.

intermittent pyuria. Polymorphonuclear leukocytes apparently get into tubular lumina by their own motility. This may account for the lack of histiocytes or mononuclear cells in the urine, although the latter may dominate the interstitial cellular reaction. We have seen several instances of hypertension in which white cell casts were the only clue that pyelonephritis [18] was the underlying disease. There is some possibility that glitter cells [6,7] in casts may be associated with infection, although they do not seem to be specific. Bacteria in casts are pathognomonic of renal infection. They are easily seen with phase constrast microscopy (Fig. 14) or glitter-cell stain. Granular inclusions may arise from degenerated cells, bacteria, or unknown flotsam and jetsam in the nephron stream. Some granular material takes a positive benzidine stain and has been cited as originating in red cells.[9] Doubly refractile fat bodies (cholesterol esters) may be found free in casts especially in intercapillary glomerulosclerosis with proteinuria (Fig. 2). Fat bodies may also be found in clumps or within epithelial cell inclusions (Fig. 11). We have found fatty inclusions in the urine of patients with nephrotic syndrome, Kimmelstiel-Wilson's disease, scleroderma kidney (progressive systemic sclerosis),[19] lupus, periarteritis, miliary infarction, and the recovery phase of acute renal insufficiency with tubular necrosis. Fat bodies are more numerous in the presence of hyperlipemia.

Fig. 21B.—Second stage in the development of a red cell cast. Red cells in a protein matrix are degenerating and beginning to lose their identity; hematoxylin and eosin; reduced approximately 2/5 from mag. × 400.



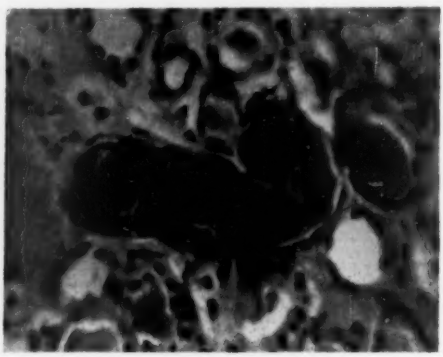


Fig. 21C.—Third stage in the formation of a red cell cast. Cells and matrix have blended into a homogenous, pigmented cast; hematoxylin and eosin; reduced approximately 2/5 from mag. × 400.

Epithelial casts are fused from desquamated tubular cells which often form in rows of two or three. Figure 22 shows the unique finding on biopsy of a compressed row of epithelial cells in a sea of interstitial edema. This may be the earliest stage in the development of an epithelial cell cast. Since the tubule as a living membrane is always replacing itself, the finding of an occasional renal epithelial cell or clump is not remarkable. However, in any disease producing damage to tubular epithelium, the appear-

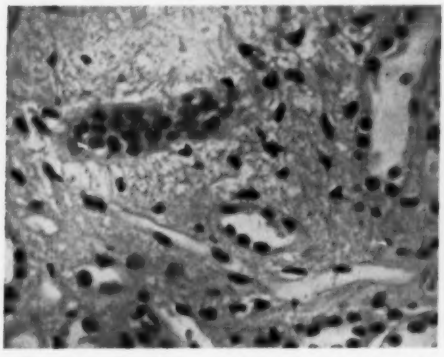


Fig. 22.—Tubular cells compressed by peritubular edema. Is this the beginning of a cellular cast? Hematoxylin and eosin; reduced approximately 2/5 from mag. × 430.

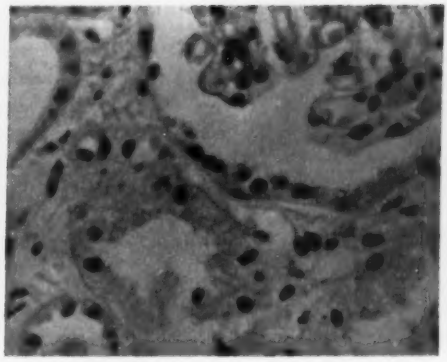


Fig. 23.—Injured, degenerating renal epithelial cells desquamating from a well-defined basement membrane. There is also a focal glomerulonephritis. The section is from a renal biopsy obtained on the 24th day following inhalation of carbon tetrachloride. The patient was a 26-year-old man (Case 2) who had nephrotoxic, acute renal insufficiency; hematoxylin and eosin; reduced approximately 2/5 from mag. × 650.

ance of many epithelial casts may indicate wholesale desquamation and sloughing. This is well illustrated by Case 1, a patient in the subsiding phase of acute glomerulonephritis. When the biopsy shows swollen edematous and degenerating tubule cells, cellular casts appear in great showers in the urine. This is also true of nephrotoxins, where the tubules may be stripped clean to the basement membrane (Fig. 23, Case 2). The degeneration of the discrete cellular cast into coarsely and finely granular material is purely a function of age and permits the inference of stasis in the nephron. Waxy casts represent the homogeneous degeneration of cells into a highly refractile, yellow cast seen most frequently in the chronic disease states with much scar tissue and tubular dilatation. Iodine staining led to the earlier designation of these casts as amyloid. However, Saleeby[20] was unable to demonstrate methylrosaniline chloride (methyl violet) staining of the material in dilated tubules of 50 patients with amyloid nephrosis. Perhaps the most significant of the cellular casts is the broad renal failure cast described by Addis,[21] who believed they were formed in the collecting tubules and ducts of Bellini and that they show variations in breadth corresponding to the diameter of lumina. He argued against their being hyaline in origin because they take up methylene blue, do not disintegrate in hypotonic solutions or even water, and resist a wide pH range. They are usually yellow and slightly granular and appear with increasing incidence in renal failure. Addis found that when almost all the casts in the urine were broad (2 to 6× narrow casts), the B. U. N. was more than 100 mg/100 ml., and the patients died in uremia.

Mucous threads appear as long strands of wavy, ribbon-like material which may show faint longitudinal striations and be mistaken for hyaline casts. They may coalesce in a form to suggest branching of collecting ducts. They are common in urine from chronic or recurrent pyelonephritis, hydronephrosis with infection, or urine with excess uric acid or calcium oxalate crystals. They may become yellow and granular in appearance from adsorption of urates. They have long been suspected to play a role in stone formation. "In certain cases in which there is evidence of considerable irritation in the kidneys, sometimes so much as to lead one to suspect the existence of calculus in the kidney, a number of flocculent shreds may be passed in the urine." (Beale,[1] p. 342)

The crystallization of spheroliths of Bence-Jones protein out of acid urine is

TABLE 2.—*Urine Sediment from the Separate Stages of Glomerulonephritis*

Acute	Nephrotic Syndrome	Chronic
Red cells	Massive albuminuria	Less albuminuria
Hyaline casts with red cell inclusions	Hyaline casts	Pigmented granular casts
Blood casts	Cellular casts, vacuoles	Waxy casts
Positive benzidine	Oval fat bodies	Broad, renal failure casts
	Doubly refractile fat bodies	

Is Telescoped in

1. Collagen kidney—periarteritis, lupus erythematosus, progressive systemic sclerosis (scleroderma), viscerocutaneous collagenosis.
2. Focal necrotizing glomerulonephritis (subacute bacterial endocarditis).
3. Rare cases in which exacerbation of chronic glomerulonephritis follows nephrotic syndrome.

an old observation.[22] While both albuminuria and Bence-Jones proteinuria occur in multiple myeloma, histologic sections show highly eosinophilic large occlusive casts in proximal [13] as well as collecting tubules and distal nephrons which are most prominent in the presence of Bence-Jones proteinuria and are believed to be composed of this abnormal, small-molecular-weight (28,000) protein. The casts (Fig. 18) are often surrounded or invaded by large cells which have been described as foreign-body giant cells or as syncytia of hyperplastic epithelial cells.[23] Amyloid deposition in the kidney may occur in conjunction with multiple myeloma, with certain suppurative and degenerative diseases, or in the atypical or primary form. Nephrotic syndrome is common with a profusion of hyaline, granular, fatty, and broad casts. Because of iodine staining, older authors frequently classified our waxy cast as "amyloid." Saleeby [20] discounted the presence of specific staining in amyloid nephrosis. However, we have seen massive amyloid infiltration in tubular basement membrane which might conceivably become part of an epithelial cast. Iverson and Morrison [24] have by staining techniques demonstrated amyloid casts in atypical amyloidosis. Myoglobin and pigmented casts, which do not stain for free iron, may be seen in urine and tubules in the crush syndrome,[25,26] in acute paralytic myoglobinuria [27] in horses and in man, and in "Haff" disease (Haffkrankheit). Any transfusion reaction, hemolytic disease, or cause for hemoglobinuria may produce large red hemoglobin casts in tubules and urine.[28] Large orange casts have been seen following infusions of globin, and cast-like objects may be seen after dextran and other plasma substitutes.

Pseudocasts are important only for their individual constituents and the confusion they may cause in distinguishing them from true casts. Tubular packing of urates can be a diagnostic aid in uric acid nephritis of gout and leukemia.

In addition to the interpretation of individual casts, certain information may be obtained from the company they keep. Red cell casts supervening on a urine with a high percentage of broad casts is, for example, suggestive of acute exacerbation of chronic glomerulonephritis or recent infarction of renal tissue. Perhaps the best instance of the value of association is seen in the telescoped urinary sediment,[29,30] the features of which are outlined in Table 2. This sediment may be seen in SBE kidney, in the various acute collagen kidneys, and with the exactly right combination of stages of glomerulonephritis.[30] We have uncovered several undiagnosed collagen nephritides by looking at the patient through a microscope.

Clinical Correlations

CASE 1.—A 9-year-old boy had been in good health until 3 weeks prior to hospitalization, when he developed the following in serial order: tem-

perature of 103 F, pharyngitis treated with tetracycline (Achromycin) for three days, skin lesions of chicken pox, recurrence of fever, reinstitution of antibiotic, one afebrile week of apparent recovery, and then nausea, vomiting, diarrhea, edema of cheeks and eyelids, massive conjunctival hemorrhages, and oliguria of 500 ml/day. On examination he had temperature of 99 F; pulse, 84; respirations, 28; B. P., 120/70. There was noted periorbital edema, enlarged tonsils with submandibular adenopathy, bilateral massive conjunctival hemorrhages, hemorrhagic areas on nasal mucosa, several healed pox scars, fine petechial, nonblanching rash on anterior neck and thorax. There was a Grade 3 systolic murmur at the cardiac apex and slight tenderness on palpation of the kidneys. The Rumpel-Leede test produced 75 petechiae in a 2 in. square and 23 fresh petechiae in a circle drawn around a quarter. The hematocrit was 32; the white cell count, 11,000, with 79% polymorphonuclear cells. The platelet count was 26,000/cubic millimeter and the L. E. preparation was negative. The hemorrhagic picture and the marked thrombocytopenia was suggestive of thrombocytopenic purpura. However, the admission urine was loaded with red cells, narrow granular casts, hyaline casts with orange polys, renal epithelial cells, and red cell inclusions. Protein excretion was 1.8 gm/24 hours, and the Addis count revealed 200,000,000 red cells and 10,000 granular casts/24 hours. The urine was sufficiently typical of acute glomerulonephritis to reassure us on the pressing question of the thrombocytopenia and made possible the prediction of a typical platelet curve for glomerulonephritis, which had the following pattern: 26,000 (6th day of illness), 31,000 (7th), 95,000 (8th), 202,000 (11th), 214,000 (15th), 306,000 (16th), 430,000 (17th), 242,000 (19th), 298,000 (22d). The normal range in our laboratory is 180,000-300,000/cubic millimeter. We concluded that the urinary sediment was invaluable and critical in establishing the initial diagnosis on this patient, who subsequently demonstrated azotemia (B. U. N., 103), diminished filtration rate (70 ml/minute), encephalopathy with convulsions, α- and β-hemolytic streptococci on throat culture, and rising antistreptolysin titer. Casts from this patient are shown in Figures 9, 12, and 13.

In acute glomerulonephritis the urinary sediment closely parallels events in the kidney. With the earliest signs of increased capillary permeability (periorbital edema) come proteinuria and many thin, long hyaline casts from the relatively undamaged kidneys. With glomerular hyperemia, swelling, and hypercellularity come hematuria, hyaline casts, with increasing numbers of red cells, orange and blue polys without bacteria as evidence for the sterile inflammatory reaction, occasional histiocytes, and fibrin strands. Blood casts appear at the height of the glomerulitis. Biopsies at this point show marked swelling to occlusion of the tubular epithelium and ragged cytoplasm. Renal epithelial cells then begin to appear in the urine, at first in hyaline casts, free, and then as epithelial cellular casts and in clumps and sheets. The desquamation is so massive and the urine volume usually increasing, that the cells appear quite fresh, as if they had been in rapid transit. There has been insufficient time for degeneration, and fat droplets and doubly refractile fat bodies are rare in these epithelial cells unless a nephrotic component is present. So great is the torrent of thousands of epithelial cells that if one watches the daily urine in the second and third weeks of the disease, one wonders what is left in the kidney. Epithelial and red cells may be seen for weeks or months during the regenerative or healing phase.

Case 2.—A 26-year-old Negro man was previously well except for moderately heavy alcoholic intake during the holiday season. He had a sudden onset of acute upper abdominal pain, rebound tenderness, hypoperistalsis, fever, leukocytosis, and anuria. He was considered to have an acute abdomen and would have been explored except for the anuria. An initial 4 ml. of urine showed only red and white cells with no casts. He was dialyzed on a Kolff-Merrill kidney on the eighth day because of fulminating uremic syndrome. With clearing of his sensorium, he remembered cleaning a hat with carbon tetrachloride in a closed room after taking a drink. Casts first appeared in the urine on the 11th oliguric day, when urine volume was 120 ml/day. They were mostly broad granular and broad waxy. Doubly refractible fat bodies in desquamated epithelial cells were first seen on the 13th day, with a urine volume of 380 ml/day. Diuresis occurred on the 15th day, and many epithelial cells and casts were excreted. Hyaline and granular casts showed faint bile staining when serum bilirubin was 1.5 mg. per 100 cc. Had the history not been obtained, jaundiced casts would have been the first index of liver damage, since jaundice was not observed preceding the discovery of bile casts. Renal needle biopsy done on the 24th day showed tubular necrosis consistent with carbon

tetrachloride poisoning. The photomicrograph is shown in Figure 23.

CASE 3.—A 15-year-old Negro youth had cyanotic heart disease since age 4. From the age of 8 he was followed in great detail by a cardiac clinic and research group, and the diagnosis was considered either tetralogy of Fallot or trilogy (pulmonary stenosis, intra-auricular septal defect, and right ventricular enlargement). Complete hemodynamic studies were done at intervals. At age 12, he developed unexplained hypertension and became less cyanotic. This was explained on the basis of a reversal of shunt. His left ventricular hypertrophy became progressive, and he developed congestive failure at 15. The urine had always been reported normal in routine hospital laboratories. We examined a urine when the patient was 15 and found albuminuria, hyaline casts with red cell inclusions, red cells, granular casts, and many doubly refractile fat bodies. A diagnosis of SBE or glomerulonephritis was entertained, but a renal biopsy was unsuccessful in yielding sufficient tissue for diagnosis. The patient was transferred to a research institute for cardiac catheterization, angiocardiography, and hemodynamic studies preparatory to cardiac surgery. All findings were consistent with tetralogy of Fallot, but no explanation was available for hypertension and left ventricular hypertrophy. Seven months later, on our second consultation, we again observed an active urinary sediment loaded with red cells and doubly refractile fat bodies. A successful biopsy revealed subacute and chronic glomerulonephritis. Renal function was severely impaired. The urine sediment in this case gave us the vital clue to a puzzling diagnostic problem.

Summary

Urinalysis is the most frequently indicated and useful laboratory test for office and hospital.

A urinary cast is a valuable and readable message from the nephron which formed it.

Methods of examination for casts are outlined, and a descriptive classification is formulated and illustrated with original photographs from routine urine sediments.

The significance of various casts and combinations in the sediment is discussed, and clinical correlations are made between urine sediments and renal pathology.

Identification of casts is a valuable case-finding technique. Casts have definite diagnostic value and lend themselves to helpful correlations with certain physiologic and anatomic events in the nephron. Casts provide an objective means for labelling the stages of certain diseases, such as glomerulonephritis, and aid the clinician in treatment and prognosis.

Dr. George Burch suggested this topic; Dr. Emanueal Bressler discussed the oral presentation; Dr. Leonard Berman read the manuscript; Gerald Rosenthal, Phyllis Straub, and Bernard Salb gave technical assistance; Edith Lauler gave help in preparing the manuscript, and many nurses, aides, and students brought a constant stream of urine bottles into the Kidney Research Laboratory.

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Acute Pulmonary Histoplasmosis

Treatment with Cortisone

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Histoplasmosis is endemic in the states of the Mississippi Valley, and it is estimated that 30 million persons have been infected with the causative fungus, Histoplasma capsulatum. Clinical cases of histoplasmosis have been reported from 25 states, and numerous epidemics have been described, often outside of the endemic areas. No effective or specific treatment has been found, but fortunately the disease does not carry a high mortality. Histoplasmosis closely resembles tuberculosis on chest roentgenograms, both in the primary and in the acute disseminated forms, as well as in the calcification resulting from healed lesions.

It is known that clinical histoplasmosis is endemic in areas coinciding with regions high in histoplasmin skin reactions. Endemic centers also coincide with areas having a high incidence of pulmonary calcification. It is also known that the soil acts as a reservoir for H. capsulatum and that soil samples collected from inside chicken houses or chicken yards are most frequently positive for the organism. Air-borne infections may be caused by inhalation of fungi spores from soil, and the inhalation of dusty material from abandoned houses, dusty silos, and storm cellars have been reported as sources of infection.

Loosli and co-workers [1] reported three members of one farm family becoming acutely ill with histoplasmosis about three weeks after all had joined in cleaning out a silo. Two sons recovered after two or three weeks, but the father required hospital treatment for seven weeks. He was gravely ill with productive cough, chest rales, fever, hepatomegaly, splenomegaly, and thrombophlebitis. In all, five months elapsed before he resumed routine activities.

Repeated surveys of the soil in the silo showed the presence of H. capsulatum. Three other members of the family had positive skin tests for histoplasmin without clinical illness. Sera from five patients showed complement-fixing bodies with the yeast-phase Histoplasma antigen. The highest titers were found in the sera of the three who had febrile illnesses.

In many epidemics, chicken or pigeon excreta were found at the place of exposure. It is felt that chickens are not carriers, but the mixture of their excreta in the soil favors the presence of the organism.

Kier and co-workers [2] reported a patient with acute pulmonary histoplasmosis who had sifted and inhaled the dust from a load of garden soil which contained chicken manure. Soil samples from the garden showed the presence of H. capsulatum. Random dirt samples taken from farms in Tennessee showed that 1.6% contained H. capsulatum, while in samples taken from chicken yards the organism was isolated in 13.7%. However, very few chickens showed evidence of infection with H. capsulatum or of antibody production. Here again it seems likely that chickens are not carriers but that areas frequented by them favor the development of the organism.

Histoplasmosis ranges in severity from slight illness lasting a few days to acute and sometimes fatal disease. A positive reaction to the histoplasmin test denotes that the patient has been infected with H. capsulatum at some time, but does not distin-

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guish between active and former disease. During the acute illness, skin tests may often be negative. Complement-fixation tests may be positive after the first few weeks of the disease and may remain so for a year or more. Symptoms of the acute disease include fever, cough, vomiting, prostration, and pneumonia, unaffected by all antibiotics. Mucosal ulcerations may occur.

Hepatomegaly may occur with splenomegaly and lymphadenopathy. Leukopenia and anemia are common in advanced involvements. H. capsulatum may be recovered from blood, bone marrow, and sputum, and cultures can be made on brain-heart infusion agar containing penicillin and streptomycin to inhibit bacterial contaminants. Lobectomy has been performed for chronic cavitary lesions in the lung and H. capsulatum cultured from the wall of the cavity.[3]

Peabody and co-workers [4] reported on the superiority of the periodic acid-Schiff stain in demonstrating H. capsulatum in resected tissue. They describe two patients with small resected pulmonary lesions histologically resembling tuberculosis in whom the true diagnosis was made when the specimens were resectioned and stained by the periodic acid-Schiff technique. A great number of brilliantly stained Histoplasma organisms were easily seen within the necrotic centers of these nodules.

As recently as 1953, Charr [5] described the 11th reported case of clinical histoplasmosis in Pennsylvania. In 1953, Aronson and Taylor [6] reported that the distribution of histoplasmin sensitivity indicated positive reactors ranging from 48% in southeastern counties to less than 10% in the northern counties. It was noted that the area of highest histoplasmin sensitivity occurs in the rich agricultural area of the Commonwealth.

Report of Cases

CASE 1.—On May 25, 1954, a white man age 27, native of central Pennsylvania, unemployed factory worker, was admitted to the Muncy Valley Hospital on service of Dr. W. E. Turner; he was acutely ill, with sudden onset of chills, fever, headache, cough, and severe vertigo. Past medical history was not significant. Physical examination of the chest revealed harsh breath sounds and coarse rales over both lungs, but there were no other important findings except that the man appeared weak and very toxic, with a prostrating illness.

Fig. 1 (Case 1).—Chest film of the father on ninth day of hospital admission shows extensive bilateral miliary nodulation.

The blood picture was normal, urinalysis negative, sedimentation elevated to 35 mm. The sputum contained mixed bacteria but was negative for tubercle bacilli; sputum culture and guinea-pig inoculation were later negative after eight weeks. Agglutination tests for typhoid, paratyphoid, and Brucella abortus were negative.

Roentgen examination of the chest on May 26, the day after admission, showed only the presence of a few fine nodular densities bilaterally in the midlung fields, but repeat films three days and one week later showed a remarkable increase of the involvement amounting to a dense nodulation throughout both lung fields, resembling miliary tuberculosis. The dense involvement persisted, but after three weeks gradually began to show clearing on serial films.

The patient's clinical course was stormy for the first two weeks, with daily temperature to 104 F, headache, rapid respiration, and cough productive of frothy mucoid sputum. Penicillin, sulfisoxazole (Gantrisin), erythromycin, streptomycin, chlortetracycline (Aureomycin), chloramphenicol (Chloromycetin), and isoniazid were given in succession and in combination without

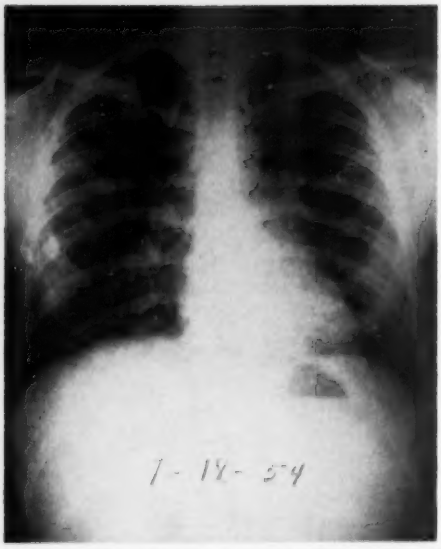

Fig. 2 (Case 1).—Seven weeks after onset of illness the chest film of the father shows partial clearing of nodulation.

apparent marked effect. Daily fever with temperature from 102 to 103 F persisted, and on the 16th hospital day cortisone in divided doses was started at the rate of 300 mg. daily intramuscularly and gradually reduced over the next two and one-half weeks. During this period the temperature steadily subsided and was normal at the time of discharge on June 29. Clinical improvement during this interval was fairly rapid, and the patient was out of bed and free from symptoms the last few days of his stay. On July 18, only a moderate number of small and fairly sharp densities remained on roentgen examination of the chest. The only complication was that of a painful phlebitis of the left leg, which responded to wet dressings, heat lamp, and analgesics.

During the second week of illness a fresh morning sputum specimen was cultured on heart-brain-infusion blood agar with penicillin and streptomycin added. At 20 days a growth of fungus was obtained which was identified on subculture as H. capsulatum. Two weeks after the patient's recovery skin tests with tuberculin, blastomycin, and coccidioidin were negative, but the histoplasmin test was positive, +2. Yeast-phase complement-fixation tests on the patient's serum were performed by Dr. Elizabeth Hazen, mycologist, New York State Department of Health, Albany, N. Y. On August 17 the titer was 12, on Sept. 1 the titer was 9, and on Oct. 7 the titer was 10. A complement-fixation test for blastomycosis was negative. Blood serum was sent to California for a complement-fixation test for psittacosis and was reported negative.

The patient's 10-year-old daughter was admitted to the Muncy Valley Hospital four days after her father. Admission symptoms were headaches, sore throat, cough, and vomiting. Temperature ranged to 104 F rectally during the first week, but subsided to normal orally in 10 days. No sputum was obtainable, blood cell counts and urinalysis were within normal limits. Roentgen examination of the chest showed the presence of a diffuse bronchopneumonia, without discrete nodulation. On serial films the process showed beginning resolution, and she was discharged on the 18th day, with complete recovery. A six-week follow-up film showed normal lung fields. Antibiotic therapy with penicillin, streptomycin, tetracycline (Achromycin) and chloramphenicol was given but without marked clinical effect. Two weeks after recovery skin tests with tuberculin, blastomycin, and coccidioidin were negative, but histoplasmin gave a positive reaction, +2.

The 2-year-old sister became ill at home with similar but less severe symptoms and recovered after 10 days without being hospitalized. One month later a skin test with histoplasmin was positive +2 and with blastomycin was negative.

The patient's wife did not become clinically ill, but a skin test with histoplasmin was +2, but negative to blastomycin. Reaction titers of 13 and 10 were obtained in the yeast-phase complement-fixation tests performed at four-week intervals by Dr. Hazen.

Inquiry into a possible source of exposure to H. capsulatum by this family gave two possibilities. The father had recently purchased a garden tractor and had plowed a number of neighbor's gardens. He recalls that several of the gardens were fertilized with chicken manure. This possibility, however, would not explain exposure to the rest of the family.

He also recalled that a few days before his illness he climbed into the attic to rescue some baby birds which had fallen out of a nest attached to the side of the chimney under the roof. He passed the young birds down into the kitchen for the children to play with for awhile before returning them to the nest.

It is conceivable that Histoplasma may have been present in the dust of the attic floor where bird droppings may have made dust a favorable medium. Without cultures from the soil or dust, however, these possibilities are only speculative.

Case 2.—On Sept. 1, 1954, a man age 54, a native of Pennsylvania, employed at the Williamsport Hospital, was admitted to that institution acutely ill, as a patient of Dr. I. DiSalvo. Onset was one week prior to admission, with chills,

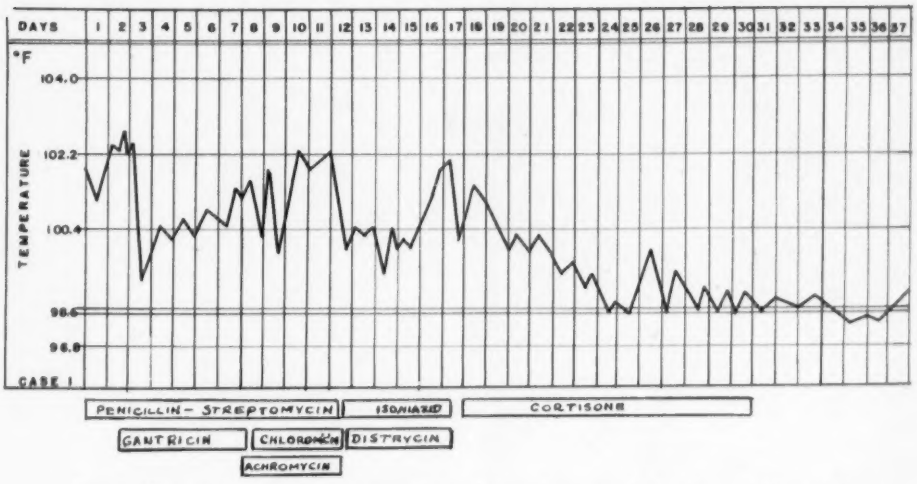

Fig. 3 (Case 1).—Temperature chart of the father shows continuing fever during administration of various antibiotic combinations and decrease in fever following use of cortisone, starting at 300 mg. daily, with gradual reduction in dosage.

fever, and malaise. He had been treated for a chest cold by his family physician. On admission his symptoms had become severer, with dyspnea, chest pain, expectoration of a mucoid material, and occasional hemoptysis. The past medical history was not significant. Physical examination of the chest revealed harsh breath sounds over both lungs and coarse moist rales. There was some dullness over the right lower lung.

The blood picture was normal; urinalysis, negative; a sputum examination contained mixed bacteria but was negative for tubercle bacilli on repeated examination.

Roentgen examination on the day of admission was reported as a marked increase in bronchial markings throughout both lungs, with a nodular infiltration suggesting a pneumoconiosis, or, likely, silicosis. Also, the possibility of a miliary bronchopneumonia, tuberculosis, or fungus infection was suggested. Repeat films four days later revealed no change in the appearance of the diffuse, nodular densities. Five days later the nodular infiltration throughout both lungs appeared to be more pronounced. A repeat film on Sept. 16 revealed no change from the previous films.

The patient's clinical picture failed to improve on tetracycline (Tetracyn), penicillin, streptomycin, erythromycin, and various combinations. The cough and expectoration of mucoid, blood-tinged sputum continued, with a daily fever with temperature ranging from 99.6 to 103 F. A histoplasmin skin test was reported as +1, while the coccidioidin skin test was negative. Culture of the sputum on admission resulted in a growth of fungi by Sept. 20, which was identified as H. capsulatum.

On Sept. 22 the patient was started on cortisone in divided doses, at the rate of 300 mg. daily for three days, then 200 mg. for four days. His temperature subsided within 24 hours of the onset of treatment, and clinical improvement was rapid. The drug was stopped for a period of 24 hours, at which time a temperature elevation to 101 F

Fig. 4 (Case 2).—Chest film taken on day of hospital admission reveals bilateral miliary nodulation closely resembling the involvement in Case 1.

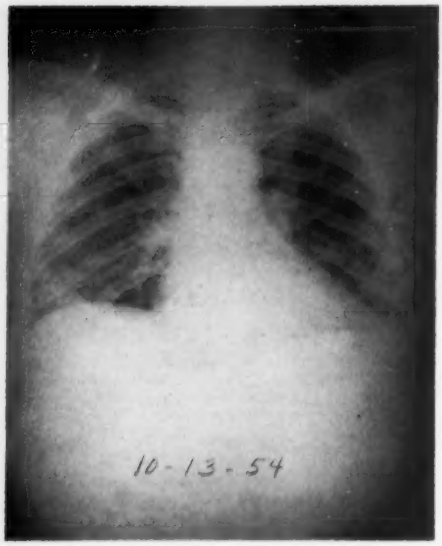

Fig. 5 (Case 2).—Chest film taken seven weeks after onset of illness shows considerable clearing of involvement.

occurred. Cortisone was again given, 200 mg. for one day, then in dosages of 100 mg. daily for the next seven days. A repeat routine chest film after the first week of cortisone therapy revealed an improvement over the examination two weeks previously.

The only possible exposure in this case, from the patient's history, must have been during the week-end visits made to a nearby farm for several months. On no occasion did he spend more than a few hours at this place.

Comment

The occurrence of two proved cases of acute pulmonary histoplasmosis with strong presumptive evidence of three other infections in one family in north central Pennsylvania is of interest for several reasons. Histoplasmosis should be considered in any acute pulmonary infection which does not respond to antibiotics and in which the diagnosis is not apparent by ordinary means.

The fact that acute histoplasmosis may be found outside of the previously known endemic areas should make physicians everywhere alert to the possibilities of this disease.

Israel and co-workers[7] warned against the use of cortisone in pulmonary mycotic infections and reported an aggravating effect of cortisone on a case of blastomycosis.

Schwartz[8] suggested the administration of corticotropin (ACTH) as a therapeutic trial to be used as a life-saving measure in the presence of histoplasmosis with high fever and severe toxemia, since there is no other specific form of therapy available at this time. He noted that a search of literature had not revealed any instance of the use of corticotropin or cortisone in acute histoplasmosis. He suggests that a parallel may be drawn from the prompt reduction of fever and toxemia in acute infections with viral and bacterial agents, following the administration of this therapy.

In both the present cases cortisone was reserved until after the first two weeks of illness. It is suggested that delayed use of cortisone might reduce inflammatory reaction and toxicity at the time when the patient's immunity might be established. Immediate use of cortisone might have the adverse effect of furthering spread of infection and of suppressing antibody formation. On the other hand, if sufficient time has elapsed for a good antibody response, it might be justifiable to use cortisone in patients with severe pulmonary infections, continuing marked toxemia, and fever. Trial of cortisone under these conditions might shorten the course of illness, or perhaps prove life-saving.

Summary

The use of cortisone in two cases of acute pulmonary histoplasmosis with apparent benefit is outlined.

A family epidemic of pulmonary histoplasmosis occurring in north central Pennsylvania is described.

The possibility of histoplasmosis in any severe pulmonary infection is stressed and should be considered.

The cautious further trial of cortisone as a possible aid in recovery from histoplasmosis is recommended.

The use of cortisone should be reserved for those cases with continuing toxemia and

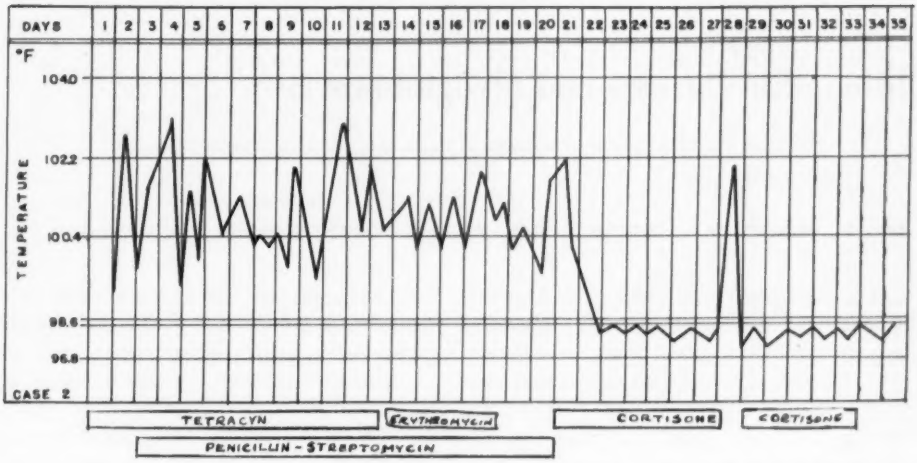

Fig. 6 (Case 2).—Temperature chart indicates persistence of fever in spite of antibiotics, until cortisone was started after three weeks of illness. Flare-up of fever was noted when cortisone was stopped for one day, with further progressive reduction as cortisone was resumed.

severe prostration, and it should not be used until time has elapsed for adequate antibody formation.

Devitt's Camp.

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Idiopathic Paroxysmal Myoglobinuria

Detailed Study of a Case Including Radioisotope and Serum Enzyme Evaluations

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The liberation of myoglobin pigment from striated muscle and its subsequent appearance in the urine is a dramatic, potentially serious, and fortunately rather rare occurrence. Many types of traumatizing damage to muscle fibers may cause a partial or complete dissolution of the muscle sarcoplasm with the release of myoglobin and probably many other of the intracellular components. Some of these substances enter the circulation, and myoglobin, at least, is excreted by the kidney. Hence, myoglobinuria is not associated specifically with any single disease process but is a sign of severe damage to a significant mass of striated muscle.

In addition to the traumatic myopathies, there have been reported a number of cases of myoglobinuria, usually recurrent and unassociated with any traumatic or toxic event. About one-third of these have been associated with muscular dystrophy. The remainder of the cases, 20 in number, have been idiopathic and unassociated with any specific or at least constantly recognizable disease process. This report deals with such a case, a man who throughout all of his adult life has suffered from recurrent major and minor attacks of myoglobinuria.

Although the pathophysiological mechanisms underlying this disease entity are still not understood, we have been able to conduct a number of studies not previously reported on this condition. The results, together with some recent reports on the physical chemistry of myoglobin, allow us to formulate a fairly clear picture of a number of the events which occur during the course of this disease. To add further emphasis to the potential seriousness of the disorder, our patient, as have others, developed acute renal shutdown following his induced acute attack. Recovery from this was fortunately most satisfactory.

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Report of a Case

A 57-year-old white male office worker of Scotch and American Indian ancestry was first admitted to the Wadsworth Veterans Administration Hospital on Feb. 16, 1955, with mild symptoms and chemical evidence of diabetes mellitus. History revealed that he was perfectly well and healthy until the age of 20. Muscular effort including strenuous wrestling in matches prior to this time cause him no discomfort. While in France, in 1918, (age 20) he began to experience aching and cramping in the calves following moderate forced marching with a light pack. On the third such occasion the cramps were so severe that he had to be carried back to the camp. After this episode he noted that any muscle or muscle group would react in the same way with pain, tenderness, and cramps following heavy physical exertion. The cramps would last up to 12 hours and the pain and tenderness up to 48 hours. The quadriceps muscles were most frequently affected. In 1922, following heavy lifting, he developed lumbar pain and muscle cramping which was followed by the passage of dark red urine for the first time. On many occasions since then he has experienced this sequence of events, and the passage of red urine has followed overexertion of any significant bulk of muscle or muscle groups. He estimates that he has had at least 50 "major" attacks during which he excretes heavily colored red urine over an 8- to 12-hour

TABLE 1.—*Serial Urine Findings Before and After Exercise*

Time, Hr.	Vol., Cc.	Color	pH	Specific Gravity	Protein	RBC/ HPF	Guaiac Reaction	Urine Hemoglobin, Mg./100Cc.*	Hemoglobin Excreted/Hr., Mg.
−1½	180	Light yellow	9.0	1.010	0	0	0	0	0
0	Exercise initiating an acute attack								
+1½	515	Light yellow	9.0	1.008	1+	2-3	1+	8.0	27
+2	125	Faint pink	7.4	1.005				28.0	70
+3	150	Pink	7.0	1.010				43.6	66
+4	150	Light red	7.0	1.009	2+	2-3	3+	63.0	95
+5	100	Red	6.5	1.014				98.0	98
+6	105	Dark red	6.0	1.014	4+	2-3	4+	----	----
+7½	130	Dark red	6.0	1.014	†			208	180
+10½	105	Red brown	6.0	1.016				----	----
+13	50	Red brown	6.0	1.017	4+	6-8	4+	285	57
+24	20	Chocolate brown	5.0	1.022	4+	10-12	4+	----	----
	1,450								

* Aliquot of combined 24-hour urine specimen contained 100 mg./100 cc. of hemoglobin.
† Protein 940 mg./100 cc. at 7 hours.

span. He also believes he has had several hundred "minor" attacks, which are brought on by submaximal exercise, producing mild muscular cramping often followed by excretion of pale pink urine for a short time. In this connection, he has been able to abort many attacks by massaging and placing at complete rest any muscle group which begins to cramp. In the past 15 years he has noted a tendency to develop the symptom-complex on less and less exertion and has suffered some attacks after merely kneeling for less than a minute in his garden (quadriceps cramps), lifting a heavy object (biceps and pectoral cramps), etc. Except for the association of exertion or strain with the attacks there has been no other significant symptom preceding, during, or following them. There are no associated chills or fever, no excessive thirst or urination, and no cardiovascular or cerebral symptoms.

In general, this man has been in excellent health. He had no significant prior illness and no operations or serious injuries. He has worked for years in a sedentary office job, and there has been no known exposure to toxins or chemicals.

There is no family history of any remotely similar disorder. His father died at the age of 89 and his mother at age 65. Six siblings, ages 65 to 80, are at present quite well.

In 1950 he was admitted to an Army Hospital in Hawaii, where detailed studies were conducted and the diagnosis of myoglobinuria was proven spectrophotometrically for the first time. A diabetic glucose tolerance curve was noted, although the fasting blood sugar was normal. An attack was induced by exertion and was followed closely by several analyses of serum calcium, potassium, phosphorus, creatine, creatinine, and carbon dioxide. In general, these revealed no significant alteration.

Physical examination at the present admission revealed a healthy-appearing, somewhat obese white man. The blood pressure was 140/85. There was no evidence of muscular atrophy, but the musculature was somewhat flabby. Muscle strength tests were not completely carried out because of the tendency to initiate cramps in the contracted muscles. In general, however, there was no evidence of significant impairment of muscle power. There was no sensory alteration. The remainder of the examination was negative.

The routine laboratory data were normal except for an elevation of the fasting blood sugar to 122 mg. per 100 cc. A typical glucose tolerance curve was recorded. The serum hemoglobin was normal on two occasions, and an I^{131} uptake was normal. Liver function studies were normal. The fecal urobilinogen output was 34 mg. per day. Red cell fragility tests as well as a direct Coombs test and the Donath-Landsteiner reactions were negative. The ECG showed a left bundle-branch block. Findings on muscle biopsy done on the right quadriceps femoris muscle were within normal limits (there had been no muscle cramps in this thigh for four years). An electromyographic study was normal.

Course and Procedures During and After Exertion.—After extensive baseline studies (Tables 1-3) the patient was given sodium bicarbonate in doses of 2 gm. every 4 hours for 16 hours to alkalinize the urine. In a fasting state, on the morning of April 20, 1955, an episode of muscular cramping was induced. This was done simply by having the patient crouch beside the bed with the knees and back well flexed so that the anterior thigh muscles were placed under stretch and tension. In 20 seconds he reported beginning cramps in both thighs, and in 40 seconds he could no longer tolerate the discomfort and was powerless

TABLE 2.—*Serial Hematologic Values Pre- and Postexercise*

	Preexercise	Brief Exercise Period	Postexercise				
			30 min.	2 hr.	6 hr.	26 hr.	48 hr.
Hgb., gm./100 cc.	15.8			16.8	16.8	15.8	14.9
PCV., per cent	48			49	51	49	45
Rbc, ×10⁶	5.0				5.4	5.1	4.8
Wbc.	8,900		6,200	7,100	7,500	7,100	8,100
Polymorphonuclear leukocytes, per cent	79		76	80	74	81	80
Lymphocytes, per cent	20		21	19	21	19	18
Platelets, ×10³	406				540		470

to arise. He was lifted into the bed, and examination disclosed firm spastic contracture in all portions of both quadriceps femoris muscles. Also the right pectoralis major muscle and the right triceps were moderately cramped and firm. The latter muscles were apparently affected when the patient attempted to catch and brace himself as he began to fall while crouching. The involved muscles were moderately tender at the onset and became more tender after several hours, when they were swollen and firm. There were no immediate systemic reactions other than those associated with the discomfort. The thighs were immovable because of pain and spasm for the following seven hours. Relaxation then began to occur, but weakness, tenderness, and swelling persisted in the anterior thighs for several days.

Urine specimens were collected at frequent intervals after the development of muscular cramps. Collections during the first two hours after exercise disclosed no color alteration. The one-and-one-half-hour postexercise specimen showed a small amount of albumin. The two-hour urine specimen had a faint pink coloration, and hourly collections from this time on disclosed a progressive deepening of the pink to a red, dark red, red-brown, and chocolate-brown color in 10 hours. Figure 1 illustrates this transition. Throughout the attack the serum remained clear, as demonstrated by the specimen obtained between the 8th and 10th hours (Fig. 1). In Table 1 the serial urinary findings are recorded. It is to be noted that the urine showed a strongly positive guaiac reaction in the virtual absence of microscopic red blood cells.

In Table 2 several hematologic procedures are reported. The serum hemoglobin values did not vary significantly during the 48 hours after the onset of the attack. There was no leukocytosis or

TABLE 3.—*Serial Blood Chemistry Values Pre- and Postexercise*

	Preexercise	Brief Exercise Period	Postexercise							
			10 min.	30 min.	2 hr.	5 hr.	8 hr.	12 hr.	26 hr.	48 hr.
Blood urea nitrogen*	12			12			12	13	24	40
Creatinine*	0.7			0.9	0.9	0.9	0.9	1.4	2.3	5.4
Glucose*	142			94	90	74			174‖	
CO_2†	15		19.8	17.6	21.5	22.8		19.0	17.6	23.7
Sodium†	142			147		153		146	135	138
Potassium†	4.9			5.8		4.6		5.5	6.1	5.2
Calcium*	9.8								9.2	10.0
Phosphorus*	3.6								6.9	5.8
Chloride†	105			100		108		100	97	93
Total protein‡	7.45									6.1
A/G values‡	4.02/3.43									4.3/1.8
Bilirubin Total*	0.48			0.62			0.86		1.24	
Direct/Indirect*	0.28/0.20			0.28/0.34			0.32/0.54		0.62/0.62	
Serum iron§	140			205	170	170			160	260
Pyruvic acid* ¶	2.22		2.17	2.04	3.37	1.74	1.98		2.20	
Lactic acid* #	19.34		24.80	28.85	26.65	26.31	43.16		28.47	

* Mg/100 cc.
† mEq./liter.
‡ Gm./100 cc.
§ γ/100 cc.; normal adult male values in this laboratory, 125-238 γ/100 cc.
‖ After intravenous dextrose.
¶ Normal pyruvic acid 0.44 to 5.50 mg./100 cc.
# Normal lactic acid 20.0 to 40.0 mg./100 cc.

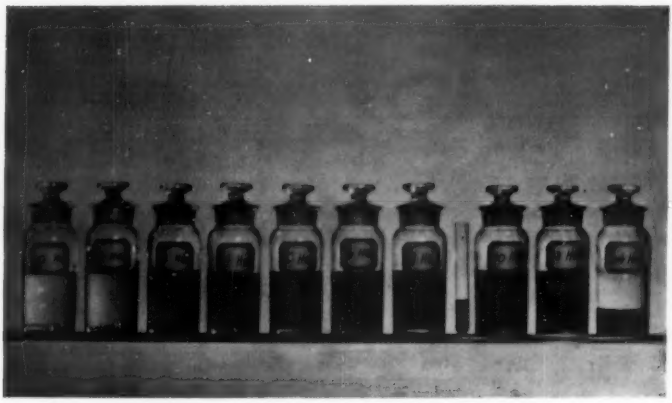

Fig. 1—Serial samples of urine collected at time intervals as indicated following muscular exertion. Note the serum sample (small tube) of normal color which was obtained at the ninth hour.

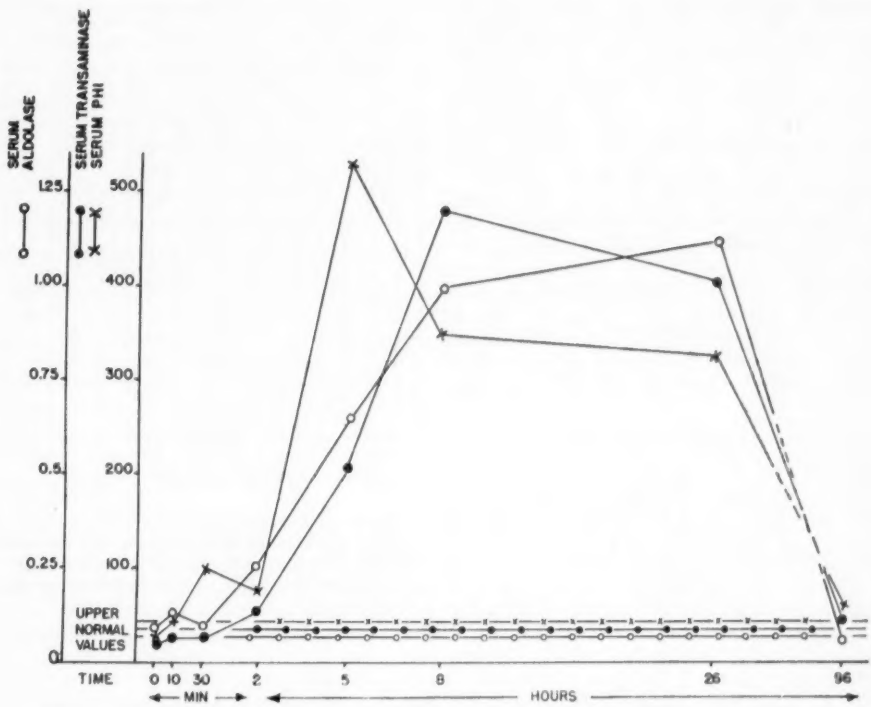

Fig. 2.—Graphic representation of the progressive elevation of the serum glutamic oxalacetic transaminase, aldolase, and phosphohexoisomerase after initiation of an episode of muscular cramping. The normal levels for these serum enzymes are also charted. For details of these studies and the methods of enzyme determination see the text.

alteration in the polymorphonuclear/lymphocyte ratio during the attack.

Serial routine blood chemical analysis and special studies of a few constituents are listed in Table 3. In general, there was no significant alteration in any of the routine tests, including serum potassium and glucose. Beyond 24 hours after the induced attack the blood urea nitrogen and serum creatinine rose moderately. This was most probably the result of the diminished renal output at this time rather than a specific effect of the muscular injury, for, as will be noted later, during the 24 hours after exercise the urine creatinine output was actually lower than normal. Hence, at least during this time interval, less was liberated from muscle. The moderate elevation in serum bilirubin from the second day onward was probably due to the continued release and degradation of iron-containing pigment from the affected muscles. It is of interest to note that there was no significant alteration in the values of the serum pyruvic acid or lactic acid during the acute stages of the attack. These substances are frequently elevated after muscular exertion but apparently not after muscle tissue breakdown. The electrophoretic patterns of the serum proteins were normal and were identical before and after exercise.

The levels of three measurable serum enzymes, each known to be present in muscle tissue, were studied serially. These enzymes were the glutamic oxalacetic transaminase, aldolase, and phosphohexoisomerase (PHI).* Figure 2 records the progressively marked elevation of all three of these substances to levels 10 to 20 times their normal values. It is interesting to note further that on the fourth day the value of all these substances had returned to near normal despite the fact that renal output was almost negligible at this time. This indicates that the dissipation of these enzymes is not dependent on the integrity of renal function.

Visible absorption spectra of several urine specimens and blood sera were obtained with use of a

* Glutamic oxalacetic transaminase was determined by the method of Karmen, Wróblewski, and LaDue,[7] aldolase by the method of Beck,[8] and PHI modified slightly from the method of Bodansky.[9]

recording spectrophotometer.† Photography of the tracings obtained are shown in Figures 3, 4, 5, and 6. The characteristic maxima at 582 mμ and minima at 564 mμ of oxymyoglobin were demonstrated in the urine (Curve 2, Fig. 3, and Curve 1, Fig. 5). These curves were compared with others of the patient's hemolyzed red blood cells (Curve 4, Fig. 3) and demonstrate the slight leftward shift of the maxima (577 mμ) and minima (560 mμ) typical of blood oxyhemoglobin. The addition of potassium ferricyanide abolished the peaks at 582 mμ and 577 mμ of myoglobin and hemoglobin, respectively, and broadened the band at 540 mμ (Curves 3 and 5, Fig. 3). This is typical of cyanmetmyoglobin and cyanmethemoglobin. In the initial postexercise urine specimens shallow rises were noted at 500-510 mμ and 636 mμ. In the 20-hour postexercise specimens, when the urine was chocolate-brown in color (Fig. 1), these bands were much more prominent (Fig. 4). Evidence that they represented a progressive increase in the concentration of metmyoglobin is seen in curve 2, Figure 5, where ferricyanide was added to the five-hour postexercise urine. Here

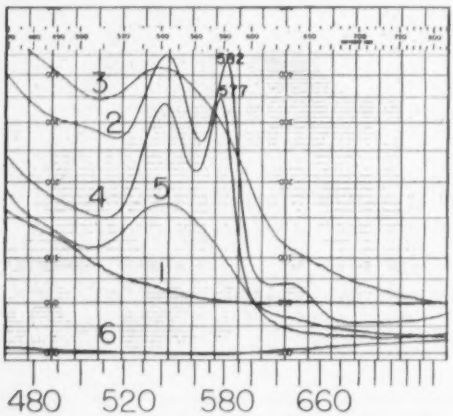

Fig. 3.—Photographed recording of the visible absorption spectra of centrifuged urine specimens. Abscissa, wave length in millimicrons. Curves represent analysis of 1. Undiluted control urine; 2. four-hour postexercise urine diluted 1:1; 3. four-hour postexercise urine diluted 1:1 plus $Fe(CN)_6^{-3}$ and KCN: 4. patient's hemolyzed red blood cells diluted 1:100; 5. patient's hemolyzed red blood cells diluted 1:100 plus $Fe(CN)_6^{-3}$ and KCN; 6. empty cuvette. See text for more detailed descriptions.

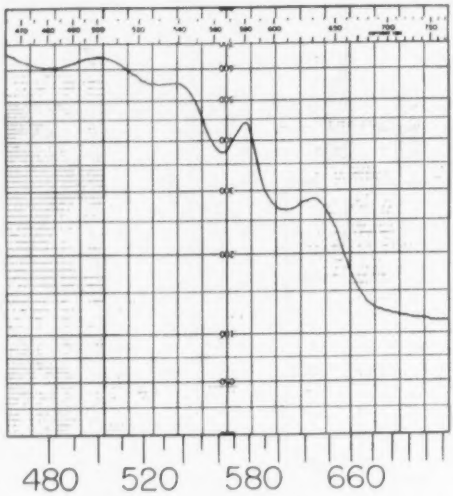

Fig. 4.—Thirteen-hour postexercise urine showing relative increase in metmyoglobin (λ maxima=500-510, 636 mμ) and decrease in oxymyoglobin (λ maxima=542, 581 mμ; λ minima=564 mμ).

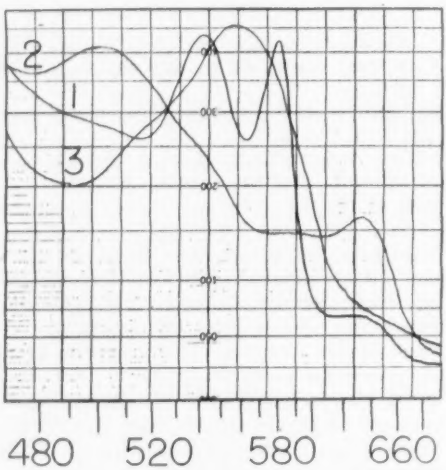

Fig. 5.—Demonstration that the 500-510 and 636 mμ bands in the patient's urine are due to metmyoglobin. The curves represent 1. Four-hour postexercise urine diluted 1:1 (λ maxima 582, 500-510, 636 mμ) (λ minima=564 mμ); 2. urine plus $Fe(CN)_6^{-3}$ shows λ maxima=500-510, 636 mμ, which is characteristic of metmyoglobin; 3. urine plus sodium hyposulfite shows λ maxima=560 mμ, which is characteristic of reduced myoglobin.

† The spectrophotometry was done in a Beckman Model DK Recording Spectrophotometer, using 1.0 cm. silica cuvettes at 26 C. Wave-length scales were newly calibrated with a mercury discharge lamp to tolerance of less than 0.6 mμ.

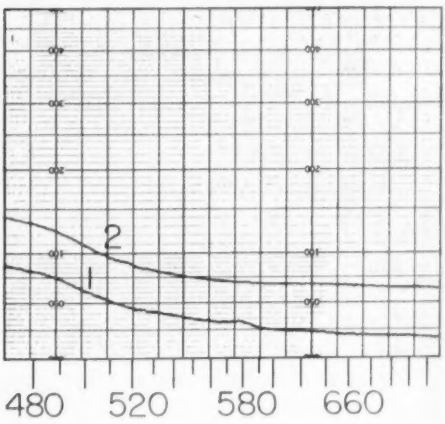

Fig. 6.—Visible spectra of 1. control plasma and 2. 9-hour post exercise plasma. Both were diluted 1:15.

the previous peaks were abolished with an accentuation of the 500-510 mμ and 636 mμ bands characteristic of metmyoglobin. Throughout the entire period the patient's blood plasma did not contain detectable quantities of either myoglobin or hemoglobin (Fig. 6).

Quantitative determinations on several urinary constituents are recorded in Table 4 for 24-hour periods immediately before and after exercise and two months later. Of significance are increase in creatine and decrease in creatinine output during the immediate postexercise period. The urinary volume of 1450 cc. during this period was adequate, and the specific gravity was fairly high, hence, it is probable that adequate elimination of these substances from the circulation by the kidney took place during this interval despite the fact that anuria was impending. The increase in creatine output presumably reflects the massive release of muscle sarcoplasmal elements among which phosphocreatine (creatine) would be a prominent substance. Creatinine, on the other hand, is normally a degradation product of phosphocreatine during muscular work. It is to be expected that the creatinine excretion would decline, since (*a*) creatine was released in large quantity and excreted intact, (*b*) the enzyme systems likely involved in many phases of the metabolism of creatine were deranged, and (*c*) the patient was inactive at complete bed rest. As recorded, the excretion of sodium and potassium did not vary significantly during any of the three test periods. The urinary porphobilinogen test was consistently negative. On an aliquot of all the combined urine excreted in the 24 hours following exercise the urinary myoglobin concentration (expressed as hemoglobin) was 100 mg. per 100 cc. With a urine volume of 1450 cc. during this 24-hour period, 1450 mg. of myoglobin was liberated through the kidneys. The implications of this will be discussed later. The maximum urine myoglobin concentration was 285 mg. per 100 cc. 13 hours after exercise. The rate of excretion of myoglobin increased progressively to a maximum of 180 mg. per hour, seven and one-half hours after exercise (Table 1). The fecal excretion of urobilinogen declined slightly from a preexercise value of 34 mg. per 24 hours to an immediate postexercise 24-hour value of 24 mg.

In Figure 7 are recorded the last of the detailed studies done on this patient. The total body exchangeable sodium and potassium were studied by the radioisotope dilution technique[4,5] with radioactive K^{42} and Na^{22} one month prior to exercise, on the day of exercise, and again two months thereafter. There are some remarkable discrepancies between the immediate postexercise values and those obtained before and long after exercise. All procedures were done carefully by the same technician on adequate specimens. Each was double checked and run against control specimens. As noted in Figure 7 there was a remarkable drop in the total exchangeable potassium and a smaller but significant rise in the extracellular and total exchangeable sodium immediately after exercise.

Subsequent Course.—It became apparent 20 hours after exertion that the renal output was declining despite adequate fluid intake. Hence, oral

TABLE 4.—*Quantitative Urinary Data Before and After Exercise* *

Date	4/19-4/20		4/20-4/21	6/22-6/23
Urobilinogen†	5.2		2.6	4.0
Creatine‡	0.253		1.984	0.032
Creatinine‡	1.356		0.684	1.081
Potassium§	69.2	Exercise	61.4	61.5
Sodium§	185.5		99.2	79.0
Total amino acids†	.....		.....	237.5

* All data are from 24-hour collections.
† Mg./24 hr.
‡ Gm./24 hr.
§ mEq./24 hr.

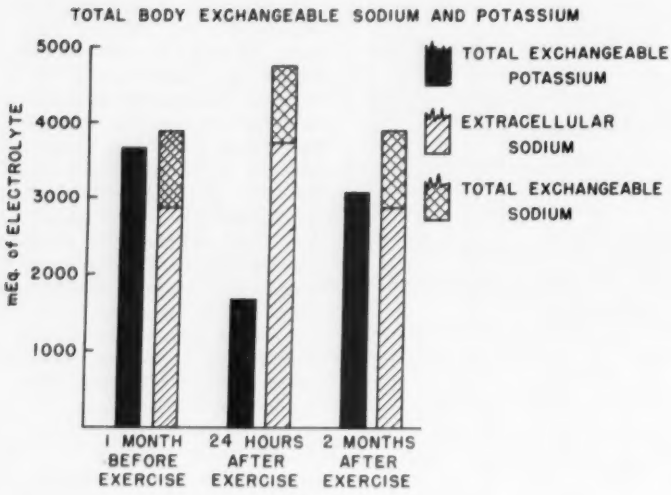

Figure 7

fluids were restricted to avoid overhydration. By 36 hours anuria was nearly complete, and it persisted for 13 days. During this time the patient was treated very conservatively with minimal parenteral fluid and electrolyte administration and other measures. During the first few days of anuria the serum creatinine rose rapidly and the urea nitrogen slowly. On the 15th day the highest observed values for creatinine, of 11.6 mg. per 100 cc., and urea nitrogen, of 156 mg. per 100 cc., were reached. Improvement was slow but continuous thereafter. The serum potassium rose to a maximum of 6.4 mEq. per liter on the 14th day. Artificial hemodialysis or other procedures were not necessary in this patient, who made a complete clinical recovery after a rather prolonged period of diuresis. He was well except for moderate generalized muscular weakness and some residual tenderness and possibly mild atrophy in both anterior thigh muscle groups by the 48th day after exercise. Urine concentration at this time could not be achieved beyond a specific gravity of 1.014. He left the hospital without medication on the 63d day.

He has been seen at intervals since that time. On a restricted carbohydrate diet his mild diabetes has been completely controlled. He has not had any further attacks of muscular cramping, but he has been most cautious in his activities and scrupulously avoids any type of exertion. He has even ceased climbing stairs, since on one or two occasions even this minimal exertion began to induce cramps in the calves or thighs. When last seen, 11 months after the acute attack, he was well and physical examination, including completed neurological review, was negative except for some generalized loss of muscular tone. The maximal urine concentration at this time was 1.024.

Comment

Apparently because of the dramatic nature of cases of this type and the interesting possibilities they present for conducting a variety of analytical procedures, a considerable number of cases of myoglobinuria have been fairly thoroughly studied and recorded in the literature within the past 10 years. At least five reviews of the subject have appeared in the past three years: Acheson and McAlpine [6]; Spaet, Rosenthal, and Dameshek [7]; Hed [8]; Berenbaum, Birch, and Moreland,[9] and Reiner et al.[10] Björck [11] has extensively reviewed the entire literature on myoglobin in man and animals.

In general it can be stated that myoglobinemia and myoglobinuria are evidences of skeletal muscle damage, but their occurrence does not constitute a single disease entity. Epidemic myoglobinuria (Haff disease) is undoubtedly the commonest cause for the appearance of muscle pigment in the urine. Epidemics primarily affecting adults and also domestic and wild animals have been reported from several areas in Europe, such as East Prussia,[12,13] Sweden,[14] and

Karelia, in Northwestern Russia.[15] The cause of this disorder is undetermined, but it is most likely a viral infection. A toxic etiology remains a possibility, but with the sporadic widely separated occurrences that it has shown, it is unlikely that a specific type of toxin may be incriminated. The outbreaks have been so transient that new cases have ceased to appear by the time definitive studies have begun.

Most of the remainder of the reported cases are associated with trauma of one sort or another. Hence, myoglobinuria has been found after severe crushing injuries to the limbs,[16] high-voltage electric shock,[17] thrombosis of an artery which supplies a large muscle mass,[18] and severe physical assault.[19]

Aside from cases obviously due to trauma, there have been reported a total of 27 cases of paroxysmal myoglobinuria.[6-10,20-35] We would agree with Berenbaum et al.[9] that Millikan's case[36] is insufficiently documented to be included in any series. The cases seen by Stokes[34] and Prankerd[35] are not recorded in detail, but in each instance myoglobin was found in the urine, and each author specifically noted the clinical absence of muscular dystrophy. We feel, as does Hed,[8] that the case recorded by Elek and Anderson[37] probably represents a form of ischemic muscle disease, likely due to trauma, exposure, and possibly obliteration of arterial blood supply to the affected calf muscles. Arterial pulses were absent in this case. One of us (C. M. P.) has had information about a similar case following our report on anterior tibial muscle ischemia.[38] In this case[53] severe lower leg muscle pain and edema followed mild trauma to the anterior tibial regions. As the patient was apparently recovering after 14 days, passive and active manipulation of the lower legs precipitated a sudden crisis, probably due to liberation of muscle breakdown products into the circulation. He died three days after this with acute anuria. At autopsy the anterior tibial muscles were soft necrotic masses and their nutrient arteries were thrombosed. Hemoglobin pigments were present in the renal tubules. Myoglobinuria was not proved in this case. In Elek and Anderson's case, surgical intervention probably precipitated the release of muscle pigment, since no coloration was noted in the urine until after operation.

Of these 27 cases, 6 have been associated with muscular dystrophy in the same patient[6,8,24-27] and one with myotonia congenita.[32] Hence, to date there has been a total of 20 adequately documented cases of truly idiopathic paroxysmal myoglobinuria (not including the present case). Of these about one-half have had myoglobin proved spectroscopically in the urine, but several unequivocal cases were reported before this test was generally available. Hed[8] has placed three of these cases into a separate group on the basis of familial relation. We would feel that until more cases are reported and a further understanding of the basic lesion is at hand such a special grouping is unnecessary. The separate classification of cases associated with muscular dystrophy, however, is reasonable, since they represent examples of liberation of muscle-cell contents secondary to known disease of the muscle fibers. The same applies to the two cases of myoglobinuria associated with dermatomyositis reported by Günther[39] and Paul[40] and the case associated with myotonia congenita.[32]

The severity of this disease may be judged from the fact that 6 of the 20 cases died as a result of their disease,[18,24,28,30,31,33] usually in acute renal shutdown, and four of the remainder survived bouts of severe anuria—Spaet, Rosenthal, and Dameshek's[7] case with the aid of the artificial kidney, and one case of Reiner et al.[10] after peritoneal lavage.

The chemistry of myoglobin is now fairly well understood. It has a molecular weight of about 16,800,[36] or one-quarter the weight of hemoglobin. It has one atom of iron per molecule, whereas hemoglobin has four. The globin protein fractions differ somewhat in the two substances and account primarily

for the weight of the molecules. Because of its smaller size myoglobin passes the glomerular membrane fairly readily and has a renal threshold of 15 mg. per 100 cc. of blood, in contrast to a threshold of 100 to 150 mg. per 100 cc. for hemoglobin.[41] This differential accounts for the fact that myoglobin may color the urine when the plasma is clear, whereas whenever hemoglobinuria is present the plasma is likewise colored. From our observations it appears that a concentration of myoglobin in the urine of about 25 mg. per 100 cc. is necessary to give a faint recognizable pink color to the urine.‡

In the past, laboratory studies during the acute or quiescent stages of idiopathic myoglobinuria have failed to disclose the mechanisms behind the disease process. In carefully studied cases there has been no consistent deviation in any of the serum electrolytes, glucose, lactic acid, pyruvic acid, creatine, creatinine, or protein fractions. Much has been made in some quarters about the not infrequent association of diabetes mellitus or abnormal glucose tolerance tests with this disease. Some analogies have been drawn with a somewhat similar disease in horses, equine myoglobinuria, which can apparently be initiated after a period of rest and a high carbohydrate diet. This disease is supposed to be due to rapid and excessive breakdown and liberation of muscle glycogen.[42] Among the human cases there have been several without detectable abnormality of glucose metabolism, and, as speculated by Berenbaum, Birch, and Moreland,[9] disturbances of carbohydrate metabolism are probably more the effect than the cause of the muscle disorder.

Laboratory studies on urine, on the other hand, have revealed a fairly consistent rise in excretion of creatine and decline in creatinine during an acute attack. Except for the total unexplainable absence of creatinuria in all stages of the disease in the case of Spaet et al.,[7] the creatine levels have consistently risen following precipitating exercise. In the present case nearly 2000 mg. was excreted in the 24 hours after exercise (normal 0-60 mg. per 24 hours in adult males [43]), the highest value of all recorded cases. In line with what is known of the metabolism of creatine and creatinine, such a release of the former substance would not be unexpected considering the amount of muscle damage.

In consonance with the unaltered serum electrolyte values, the daily urinary excretion rates of sodium and potassium were essentially unaltered during any phase of the disease. The appearance of protein, occasional casts, and red blood cells in the urine during the acute attack are evidence of some degree of renal damage secondary to liberated muscle products; they are not a specific part of this disease. The coloration of the urine and the increasingly strong reaction to the guaiac test are evidences of the concentration of myoglobin excreted in the urine.

Determination of the spectrophotometric pattern of the urine in this disease is the only way that the disease can be identified conclusively. The patterns observed in the present case are typical. In addition the comparison of the spectra of myoglobin with the hemoglobin from the patient's own lysed red blood cells demonstrates the essential difference in these substances as viewed spectrophotometrically. It is interesting to note that as the urine became darker in color (and renal shutdown began to develop) the concentration of metmyoglobin increased.

Berenbaum, Birch, and Moreland [9] have recently speculated that this disease may be due to the presence of an abnormal myoglobin analogous to the defect in sickle-cell disease and the other abnormal hemoglobin disorders. No studies were carried out on this matter in the present case, but, fortunately, two reports have recently appeared which tend to clarify this point. Singer, Angelopoulos, and Ramot [44,45] have demon-

‡ Note Figure 1. At two hours the level of urine hemoglobin was 28.0 mg. per 100 cc., and at three hours, 43.6 mg.

strated (*a*) that the myoglobin in persons with sickle-cell disease is not different from that found in normal persons and (*b*) that there is a fetal myoglobin normally present in normal newborn infants which differs spectroscopically and electrophoretically from adult myoglobin. The fetal myoglobin is gradually replaced by adult myoglobin within the first six months of life. This situation is of course analogous to that which occurs in the hemoglobin cycle. The next obvious question, as to whether a persistence of the fetal form of myoglobin or the presence of an abnormal type is responsible for this disease, has been clarified in a recent report by Prankerd.[35] He observed no difference in the electrophoretic mobilities of myoglobin obtained from muscle biopsy tissue from a normal adult and from cases of sickle-cell disease and "paroxysmal paralytic myoglobinuria." Unfortunately no details are given concerning the latter case except that there was an absence of muscular dystrophy in the family and the patient. This apparently places Prankerd's patient into the group discussed herein.

These recent reports tend to absolve myoglobin from blame as the fundamental defect in this disease. As will be stated later, it appears that myoglobin is passively released during violent muscle dissolution and is only the visible indicator of the presence of disease. Whether abnormal myoglobin plays a part in other disease states of muscle is yet to be settled.

A few pathologic studies of affected muscle have been reported in recent years.[8-10, 29,37] Histologic alterations have been fairly uniform in these cases and have revealed marked degenerative changes several days after an attack. The illustrated sections reveal swollen, fragmented fibers, and retraction of muscle sarcoplasm into amorphous masses, leaving partially empty sarcolemmal sheaths and surrounding edema. Such a picture is histologically not specific but is similar to that noted in any striated muscle undergoing acute destructive change due to toxin, anoxia, or trauma.[46] An identical picture is found in muscle in equine myoglobinuria. In a few cases [7,8] no significant alteration has been noted when biopsy has been done on a painful area of clinically involved muscle. From this it can be deduced that all segments of a muscle may not be involved to an equal extent or, in fact, at all, to explain this discrepancy in pathologic alteration. Likely some fasiculi or portions of muscle are damaged to a greater degree than are others. Certainly to explain the liberation of such large molecules as myoglobin and muscle enzymes (see below) a severe injury with a great increase in membrane permeability must occur to some muscle fibers. In keeping with the idea that foci of muscle are preserved even within one muscle group is the observation that patients may be able to use the recently affected muscles with apparent near normal strength within several days of an attack. Adult muscle does not functionally regenerate this rapidly.

In our case a muscle biopsy was done on an anterior thigh muscle two months before the induced attack. No biopsy was done after the acute exertion because of the development of the complicating anuria. The preexercise biopsy was essentially normal in microscopic appearance. This is interesting, especially since the patient had experienced in the past a number of severe attacks involving these muscles. It is known that muscle fibers may regenerate quite completely if their sarcolemmal sheaths are not disrupted.[47] From experimental work on muscle trauma and regeneration [47,48] it appears that the following sequence of events may occur in muscle so damaged in an acute attack of this disease: (*a*) immediate release of many soluble products of muscle sarcoplasm, (*b*) phagocytosis of residual contracted insoluble muscle framework, (*c*) regeneration of many muscle fibers with intact sarcolemmal sheaths during subsequent weeks from viable remnants of muscle sarcoplasm or from viable ends of muscle fibers, (*d*) some fibrosis and loss of muscle tissue in areas where sarcolemmal sheaths

are disrupted and hemorrhage has occurred. This chain of events would allow for repeated recovery following severe attacks even to the same muscle groups, with gradual fibrotic replacement.

Berenbaum, Birch, and Moreland [9] have reported rather extensive histochemical studies on a specimen from an involved and extensively degenerated muscle in their case. glycogen and a number of enzymes of mus- There was a decrease or complete loss of cle. An accumulation of esterase-positive material was noted in most degenerating fibers. The significance of this is unknown.

No previous observations have been made on the distribution patterns of whole body sodium and potassium in this disease. Using the radioactive dilution technique, one of us (W. H. B.) in association with others has studied a number of patients with muscle disease by these techniques. Results in muscular dystrophy have tended to show diminished total body exchangeable potassium levels and essentially normal extracellular and total body exchangeable sodium.[49] In the present case an interesting and unexplainable pattern was observed (Fig. 7). The 24-hour dilution samples run one month prior to exercise and two months after exercise disclosed almost identical normal values. The immediate postexercise 24-hour specimen disclosed, on the other hand, a sharp fall in the exchangeable potassium and a slight rise in the exchangeable sodium. These results cannot be explained by increase in excretion of potassium or retention of sodium, for, as already noted, the total urinary excretion of these electrolytes remained relatively constant. The reasons for the unpredictable results can only be speculated upon, but they could be due to a sequestration of a large quantity of potassium (and water) in the swollen edematous damaged muscle tissue with relatively little interchange with the general body potassium pool. The moderate elevation in body sodium cannot be explained so readily.

Glutamic oxalacetic transaminase, aldolase (zymohexase), and phosphohexoisomerase (PHI) have all been isolated from animal muscle in various degrees of purity. These enzymes are confined to the cell except for low levels found in the serum under normal conditions. Fairly reliable methods have been devised for the measurement of these substances in serum and other body fluids, but their alterations, if any, in these extracellular environments in disease have only been investigated to a limited degree. Materials and equipment were available to conduct such studies in our laboratories according to revised methods suggested by one of us (W. S. B.). As depicted in Figure 2 the high levels to which all three of these enzymes rose within a few hours following the attack of muscular cramping attests to the fact that a severe internal derangement and liberation of muscle cell contents had taken place. The molecular weight of rabbit muscle adolase is about 147,000,[50] almost nine times the molecular weight of myoglobin. Presumably the other two enzymes have similar molecular weights. The demonstration of the liberation of such substances, which undoubtedly come from the damaged muscle, is good evidence that profound damage has occurred in the involved muscle tissue. It also points up the fact that myoglobin is only one of probably many substances released under such conditions, and it is likely that, could they be satisfactorily measured, almost the entire contents of the injured muscle tissue could have reached the circulation. The other question that these findings raise is this: May one or a combination of several toxic products, possibly including myoglobin, be responsible for the renal injury? No detectable quantities of any of these three enzymes were found in the postexercise urine. Green and Stoner [51] have investigated one phase of this whole problem and have related shock and other severe reactions to the release of adenosine and other nucleotides following tissue damage. We did not attempt to evaluate these substances in our patient, but conceivably they would have been elevated if looked for.

The amount of muscle tissue deprived of its myoglobin can be roughly estimated from the following facts. During the 24 hours immediately after exercise a total of 1450 mg. of myoglobin was excreted in the urine. Granick [52] has stated that the total myoglobin content of the average male is about 40 gm. A number of investigators have estimated the normal muscle bulk in adults to comprise 42% of the body weight. This patient weighed 160 lb. (72.6 kg.), and by simple calculation it can be concluded that about 2½ lb. (1.1 kg.) of muscle tissue was deprived of its myoglobin.

Myoglobinuria must be differentiated principally from the various hemoglobinurias and from porphyria, all three of which under the proper circumstances will impart a red or red-brown color to the urine. Although the final identification of these substances depends on spectrophotometric analysis, a reasonable conclusion can be arrived at by several simple laboratory tests which depend on (*a*) the renal threshold of these substances, (*b*) their reaction to the benzidine and guaiac tests, and (*c*) fluorescence under ultraviolet light. In Table 5 the results of these procedures are listed.

TABLE 5.—*Laboratory Differential Diagnosis of Paroxysmal Pigmenturia*

	Serum Color	Urine Color	Guaiac Test on Urine	Fluorescence of Urine
Myoglobinuria	Normal	Red to chocolate brown	Positive	None
Hemoglobinuria	Pink to red	Red to chocolate brown	Positive	None
Porphyria	Normal	Pink to red*	Negative	Present

* Color may develop only after exposure to light.

The reported data permit no conclusion as to the mechanism by which exercise induces attacks in these people. In the present case the disorder is quite generalized and apparently can involve any muscle group placed under severe stress, although in some the liability to attacks has been limited to certain muscle groups. As Spaet, Rosenthal, and Dameshek [7] have speculated, perhaps the situation in the muscle fibers in this disease is comparable to that of the defective erythrocytes in the hereditary hemolytic anemias. The fact that in the present case extreme exercise during youth did not initiate attacks and the observation that attacks have been induced by less and less effort over the years would tend to make a hereditary defect of muscle somewhat less likely.

Regardless of what the initiating mechanism may be, the subsequent course of events is now quite clear. The concept that an increased permeability of the muscle-cell membranes is alone responsible for the disease state seems doubtful. Instead during the florid stages of an attack of paroxysmal myoglobinuria there is wholesale coagulation of muscle sarcoplasm with total disruption of its internal systems. This is concluded not only from the histologic picture of a number of postattack biopsies but also by the evidence presented herein of the massive liberation of many muscle components which appear in measurable quantities in the blood. Myoglobin is only one of these components, and perhaps even a minor one, but it is a dramatic and visible indicator of the presence of a multitude of biochemical alterations which undoubtedly are occurring simultaneously. Increase in muscle membrane permeability would be inherent in any such a destructive lesion, but actual morphological disruption of the sarcolemmal membrane need not occur.

Although a variety of remedies have been recommended for the treatment of this disorder, none has been satisfactory. Prophylactic sedentary existence with subthreshold activity of susceptible muscle groups is all that can be recommended. It should be mentioned that following an acute attack almost total immobilization of the affected parts for a period of three to four weeks is advisable, since it is during this time that exercise will tear the fragile intact sarco-

lemmal sheaths which normally guide the regenerating muscle fibers. If this occurs, recovery will be far less complete.

Summary

Myoglobinuria is a sign of severe injury to a significant mass of striated muscular tissue. Aside from the traumatic varieties there have been reported 28 cases (including the present one) of paroxysmal myoglobinuria. Seven of these have been associated with a recognizable form of muscular disease and the remaining twenty-one are idiopathic.

The present report describes in detail the case history of a 57-year-old man who has had repeated episodes of myoglobinuria following exertion over a 35-year period. A typical episode was induced in the hospital in this man, and multiple detailed studies were made during the course of the acute episode. The majority of the routine hematological and biochemical determinations were not abnormal. Myoglobin was demonstrated spectrophotometrically in the urine. Of particular interest were the results of radioactive electrolyte dilution studies and those on several serum enzymes (aldolase, transaminase, and phosphohexoisomerase), which are known to be present in high concentration in skeletal muscle tissue. The measurable total body potassium dropped to a very low level soon after onset of the attack, and all three of the enzymes studied rose to levels 10 to 20 times normal in the serum.

From these results and other recent pathologic studies it can be concluded that the presence of myoglobin in the urine is only the dramatic visible indicator of the presence of a multitude of biochemical derangements which are undoubtedly occurring simultaneously as a result of severe muscular necrosis in this disease.

Drs. William S. Adams and William N. Valentine, both of the Department of Medicine, University of California Medical Center, assisted in the evaluation of the serum protein patterns and the serum lactic acid levels, respectively.

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The Effect of Reserpine upon Basal Gastric Secretion in Man

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Introduction

Experimental and clinical observations suggest that reserpine, the crystalline ester alkaloid of Rauwolfia serpentina, may stimulate gastric secretion and intestinal motility. Reserpine intravenously, in doses of 15γ per kilogram, increased the volume of secretion and concentration of HCl in dogs with vagally denervated (Heidenhain) pouches[1-3]; the stimulating effect was suppressed by an anticholinergic drug but not by an antihistaminic. Intestinal motility increased after reserpine orally and intravenously in dogs but not in monkeys or rats. Clinically, reserpine, 1 mg. intravenously, stimulated the fasting gastric secretion in 24 patients[4,5]; the presence or absence of duodenal ulcer and the control level of acidity did not influence the magnitude of the rise; the effect was apparent within 30 minutes after injection and continued for at least 4 hours. Similar results have been obtained by other investigators.[6,7] In contrast to previous findings, however, neither atropine nor methantheline bromide[7] intravenously inhibited the gastric secretory response to reserpine, suggesting a humoral or peripheral action rather than a central neurogenic mechanism.[4,5] Ubillús noted significant increases in gastric secretion after single doses of 5 mg. of reserpine intramuscularly; atropine reduced the volume response but not the acidity. The effect of reserpine administered by mouth upon gastric secretion has not been determined conclusively. The oral intake of 1.0 or 1.5 mg., twice daily, reportedly increased the output of HCl; however, the changes were not pronounced, and, in relation to the "spontaneous" variations in gastric secretion, their significance does not seem established. The volume of the basal gastric secretion and concentration of HCl did not change in 20 patients with duodenal ulcer, gastric ulcer, or functional gastrointestinal disorders given 1.0 mg. reserpine by mouth daily for periods of 7 to 210 days, usually approximating six weeks.[9,10] Reserpine, 0.75 mg. daily by mouth, did not increase gastric acidity in patients with prepyloric or duodenal ulcer.[11] The administration of relatively large amounts of reserpine has been complicated by recurrent ulcer symptoms,[12] gastrointestinal bleeding, and gastric perforation;[13,14] however, the incidence of these complications, so far as can be ascertained from the current literature, appears to be very small. The present study was undertaken to clarify further the effect of reserpine * orally and intravenously upon the fasting gastric secretion in man.

Methods of Study

Reserpine Orally.—The basal outputs of hydrochloric acid were measured for periods of two hours in the morning.[15] A Rehfuss tube was introduced and the stomach emptied completely. Continuous aspiration then was initiated with a hand syringe, specimens being collected in 15-minute periods. The volume of secretion and concentration of HCl were measured in all eight specimens; however, in accord with criteria established previously,[15] only the final 90 minutes were

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* The reserpine preparations used were provided by the following pharmaceutical companies, listed alphabetically: Ciba Pharmaceutical Products, Inc. (Serpasil), Eli Lilly & Company (Sandril), E. R. Squibb & Sons (R 2012Q), and The Upjohn Company (reserpine). This study was aided in part by grants from the Ciba, Squibb, and Upjohn companies.

utilized in the comparison of secretory effects (six gastric specimens). The blood pressure and pulse were measured at intervals; patients were observed and questioned as to side-effects. Three control studies were obtained before administration of the drug. Reserpine was taken orally in the following schedule: 0.1 mg. four times daily for 1 week, 0.25 mg. three times daily for 1 week, and 0.25 mg. four times daily for 10 weeks. All subjects were volunteers, well-known to the investigators (medical students, nurses, and laboratory personnel); faithful intake of the medication thus was assured. Gastric analyses were repeated at the following intervals during therapy: at the end of the 3d, 5th, 7th, 9th, 11th, and 12th weeks following onset of treatment. Two postdrug control gastric analyses were obtained at the end of the 14th and 16th weeks of observation, two and four weeks after the conclusion of therapy.

Reserpine Intravenously.—Gastric intubation and continuous aspiration were instituted as noted previously. After a control period of one hour, reserpine (1.0 to 2.5 mg. total dose) was given intravenously in 300 cc. of 5% dextrose in isotonic saline within a period of 30 minutes. Gastric aspiration subsequently was continued for three to six hours. The blood pressure was recorded at frequent intervals; careful observation for side-effects was maintained. Sixteen subjects were studied initially: four normal, two with gastric ulcer, five with duodenal ulcer, and five patients with vagotomy and gastroenterostomy for duodenal ulcer.

The effects of single doses of corticotropin (20 units), hydrocortisone (50 mg.), and reserpine (1.5 to 2.0 mg.) intravenously upon gastric secretion were compared in three separate tests in each of five additional patients. Basal gastric secretion was measured for two hours before the medication was administered and for six hours after the intravenous administration was begun; the reserpine was administered within 30 minutes and the corticotropin and hydrocortisone within 2 or 3 hours. As before, all secretions were collected in 15-minute aliquots and titrated individually, electrometrically with a Beckman pH meter; hourly totals were calculated from the 15-minute values.

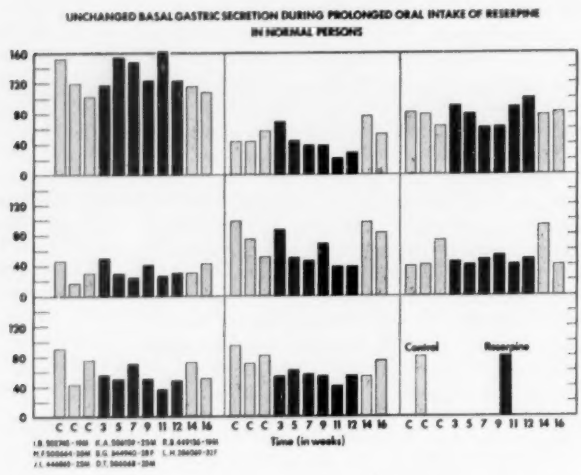
Results

A. Reserpine Orally (Table 1, Figs. 1 and 2).—The effect of reserpine orally was studied in eight subjects. Arithmetical values for volume of gastric content and concentration of acid fluctuated considerably during the control periods; however, the general pattern of acid production was maintained for each case. Gastric secretion did not change significantly except in one patient. In this case (L. H., a woman, aged 35) the volume of secretion was unaltered; however, the concentration of HCl rose significantly; the milligram output of acid for

TABLE 1.—*Effect of Prolonged Oral Intake of Reserpine Upon Basal Gastric Secretion in Normal Persons*

Patient	Sex	Age		Predrug Control			Reserpine, Wk.						Postdrug Control, Wk.	
							3	5	7	9	11	12	14	16
IB	M	19	Vol., ml.	153	119	103	117	154	148	123	164	122	115	107
			C.U.	2	0	4	5	4	5	6	1	9	4	5
			Mg.	10	0	15	21	22	27	26	6	40	17	20
KA	M	25	Vol., ml.	43	43	56	69	44	38	37	21	28	76	52
			C.U.	47	17	18	33	20	10	33	11	25	17	23
			Mg.	74	27	37	83	32	14	44	8	26	47	44
RB	M	19	Vol., ml.	81	79	62	90	79	60	37	21	28	76	52
			C.U.	42	23	13	16	28	14	33	11	25	17	23
			Mg.	124	66	29	52	81	31	44	8	26	47	44
HF	M	28	Vol., ml.	46	17	30	50	29	24	41	26	30	30	43
			C.U.	20	0	9	6	2	5	12	1	0	0	7
			Mg.	34	0	10	11	2	4	18	1	0	0	11
BG	F	28	Vol., ml.	98	75	51	87	50	46	68	38	38	97	82
			C.U.	9	22	10	9	7	9	7	23	12	1	2
			Mg.	32	60	17	25	13	15	17	32	17	3	2
LH	F	35	Vol., ml.	39	41	72	45	41	47	53	41	48	92	40
			C.U.	12	14	5	34	34	22	45	28	54	22	7
			Mg.	17	21	13	56	51	38	87	42	84	74	10
JL	M	25	Vol., ml.	91	44	75	55	51	71	51	37	48	72	45
			C.U.	2	7	16	4	2	24	26	13	17	16	11
			Mg.	7	11	44	8	4	62	48	28	30	38	18
DT	M	23	Vol., ml.	94	71	81	54	61	56	54	40	54	53	74
			C.U.	49	64	29	61	52	64	55	46	51	52	58
			Mg.	168	165	86	120	115	131	108	67	100	100	156

Figure 1


UNCHANGED BASAL GASTRIC SECRETION DURING PROLONGED ORAL INTAKE OF RESERPINE IN NORMAL PERSONS
Volume (in ml.)
Control
Reserpine
Time (in weeks)

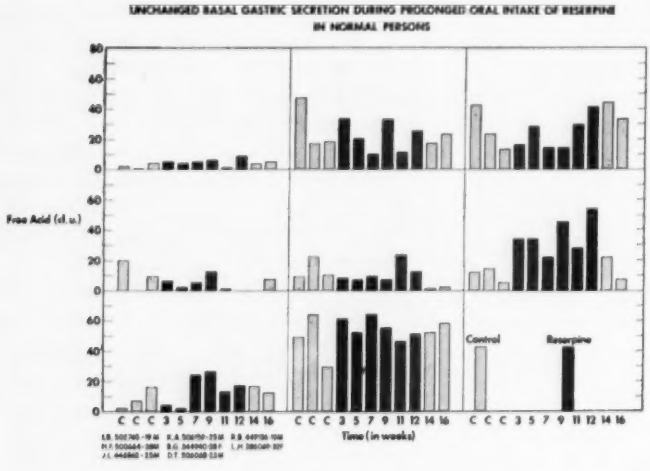

UNCHANGED BASAL GASTRIC SECRETION DURING PROLONGED ORAL INTAKE OF RESERPINE IN NORMAL PERSONS
Free Acid (cl.u.)
Control
Reserpine
Time (in weeks)

Figure 2

TABLE 2.—*Side-Effects with Reserpine Orally* *

Patient	Sex	Age	BP	P	IA	S	UF	NC	Time of Occurrence, Wk.
KA	M	25	1+	1+	3+	3+	2+	3+	BP drop 9-12; P, 11-12; others, 3-12
IB	M	19	...	1+	3+	1+	1+	2+	P drop 3-5; others, 3-12
RB	M	19	1+	..	2+	2+	1+	1+	BP drop 3-5; others, 5-12
HF	M	28	...	1+	2+	1+	1+	1+	P drop 5-12; IA, 7-12; others, 3-12
BG	F	28	...	...	2+	2+	1+	1+	S, 3-12; UF, 3; others, 3-9
LH	F	35	2+	2+	2+	2+	1+	..	BP & P drop 3-14; others, 3-12
JL	F	25	1+	1+	3+	2+	2+	3+	BP & P drop 3-12; others, 3-12
DT	M	20	1+	1+	1+	3+	1+	3+	BP & P drop 9-12; others, 7-12

* BP indicates blood pressure; P, pulse; IA, increased appetite; S, sedation; UF, urinary frequency; NC, nasal congestion; 1+, slight; 2+, moderate; 3+, severe.

each 90-minute period increased, but the increments were not pronounced.

During the four months of observation the blood pressure decreased very slightly in five patients. The pulse rate decreased slightly in six subjects; in L. H. the rate diminished from 72 to a low of 44. The commonest side-effects were increased appetite, sedation, urinary frequency, and nasal congestion (Table 2). Less frequent symptoms were diarrhea, thirst, flushing, and nightmares. All side-effects disappeared within two weeks, usually within a few days after reserpine was discontinued. The symptoms were no more pronounced in the patient in whom gastric acidity rose than in the seven persons with no change in gastric secretion.

B. Reserpine Intravenously (Table 3).—Reserpine intravenously increased gastric secretion in the four normal persons (Fig. 3), five patients with duodenal ulcer (Fig. 4), and two with benign gastric ulcer (Fig. 5). The volume rose significantly in 10, and the concentration of HCl increased markedly in all 11 persons. In one case the hourly output of HCl was augmented from a control value of 17 to 911 mg.; the rise in six patients exceeded control figures by more than 1000%. The magnitude of the elevation varied among individuals but appeared to be unrelated to the presence or absence of duodenal ulcer or gastric ulcer. The increment was smallest in one patient with duodenal ulcer (N. F.); a larger quantity of reserpine probably would have evoked a greater response. Two subjects who secreted large amounts of acid after reserpine intravenously (R. B. and I. B.) previously had not responded to the oral intake of reserpine for three months.

The five patients with duodenal ulcer who had undergone vagotomy and posterior

TABLE 3.—*Stimulating Effect of Reserpine Intravenously upon Basal Gastric Secretion in Man*

Patient	Sex	Age		Control	Hours						Dose, Mg.
					1st	2d	3d	4th	5th	6th	
AJ (Normal)	M	30	Vol., ml.	59	97	145	208	226	219	208	2.0
			C.U.	8	23	65	78	79	84	84	
			Mg.	17	81	343	761	650	670	911	
RB (Normal)	M	19	Vol., ml.	89	103	131	117	110	110		2.0
			C.U.	31	74	83	97	96	93		
			Mg.	67	278	396	413	384	372		
EP (Normal)	F	42	Vol., ml.	17	30	71	49	76	85		1.0
			C.U.	3	51	68	80	88	94		
			Mg.	2	56	176	142	243	291		
IB (Normal)	M	19	Vol., ml.	90	80	80	87	127			1.0
			C.U.	8	30	35	71	79			
			Mg.	23	87	102	225	365			
			Eosinophils	35-38		42		38			
RM (duodenal ulcer)	M	49	Vol., ml.	83	146	186	177	151	176	209	1.5
			C.U.	34	38	62	54	62	56	60	
			Mg.	103	202	420	348	341	357	456	
HG (duodenal ulcer)	M	51	Vol., ml.	73	86	109	149	139	126		1.5
			C.U.	39	67	78	92	104	99		
			Mg.	104	210	309	499	526	454		
			Eosinophils	64-72		59		60			
NF (duodenal Ulcer)	M	55	Vol., ml.	59	86	71	114	103	126		1.0
			C.U.	66	66	78	86	90	87		
			Mg.	142	207	201	357	337	399		
			Eosinophils	102-169		75		88			
FB (duodenal ulcer)	M	46	Vol., ml.	42	62	124	179				1.5
			C.U.	41	66	88	100				
			Mg.	63	149	397	651				
LH (duodenal ulcer)	M	65	Vol., ml.	88	127	216	191	270	237		2.0
			C.U.	53	74	102	82	111	126		
			Mg.	170	342	802	570	1,091	1,087		
CG (gastric ulcer)	M	45	Vol., ml.	61	51	111	126	159	110	110	2.0
			C.U.	0	0	13	38	48	54	44	
			Mg.	0	0	53	174	278	216	181	
FP (gastric ulcer)	M	44	Vol., ml.	58	90	79	129	146	133		2.5
			C.U.	8	65	89	78	89	103		
			Mg.	17	213	256	366	473	499		

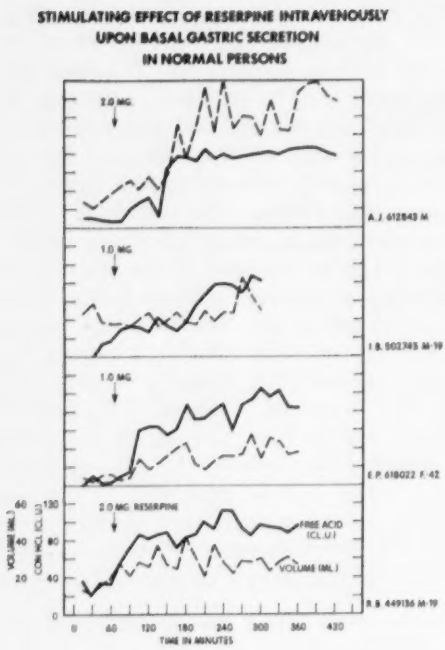


Figure 3

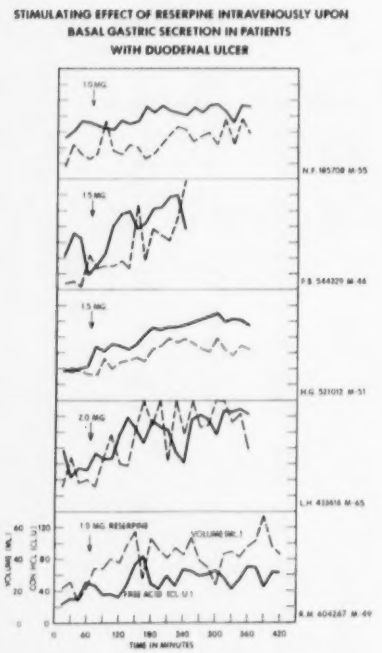


Figure 4

gastroenterostomy received reserpine intravenously in doses ranging from 1.0 to 2.0 mg. Insulin intravenously produced significant decreases in blood sugar but no rise in gastric secretion in the three persons tested, a result compatible with complete vagotomy. During the administration of reserpine, the volume of secretion rose in three cases; the concentration and output of HCl increased significantly in all five patients; the magnitude of the response approximated that of the normal and ulcer groups (Table 4 and Fig. 6).

The comparative intravenous studies indicated that corticotropin, except for three sporadic hourly increases, caused no signifi-

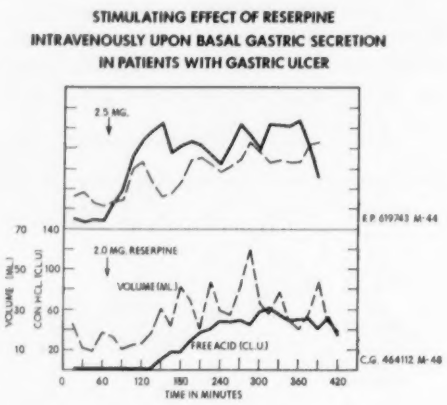


Figure 5

cant rise in gastric secretion (Table 5 and Fig. 7). Hydrocortisone stimulated gastric secretion in one patient (G. M.) for three hours; however, in another person (R. H.), the output of acid diminished significantly. In contrast to these generally negligible responses, reserpine intravenously evoked tremendous rises in the volume and acidity in each of the five patients. In one case (E. T.) the outputs of HCl rose from hourly control values of 179 and 168 mg. to 1195 and 966 mg. during the fourth and fifth hours of study.

Reserpine given intravenously to a patient with gastric carcinoma who had not responded to insulin intravenously or to

TABLE 4.—*Stimulating Effect of Reserpine Intravenously upon Basal Gastric Secretion in Patients with Vagotomy and Posterior Gastroenterostomy*

Patient	Sex	Age		Control	Hour						Dose, Mg.
					1st	2d	3d	4th	5th	6th	
JF*	M	52	Vol., ml.	71	60	125	143	102	120	123	2.0
			C.U.	35	37	80	72	72	68	58	
			Mg.	90	84	208	375	267	297	290	
RP	M	60	Vol., ml.	95	94	109	94	74			1.5
			C.U.	0	0	0	21	29			
			Mg.	0	0	0	72	78			
PM	M	58	Vol., ml.	31	62	84	96				1.0
			C.U.	0	1	17	13				
			Mg.	0	2	52	45				
HA*	M	58	Vol., ml.	81	86	99	76				1.5
			C.U.	26	28	53	56				
			Mg.	77	88	191	155				
JA*	..	..	Vol., ml.	64	55	77	58				1.5
			C.U.	31	28	26	49				
			Mg.	72	56	73	157				

*Negative gastric secretory response to insulin; other patients not tested.

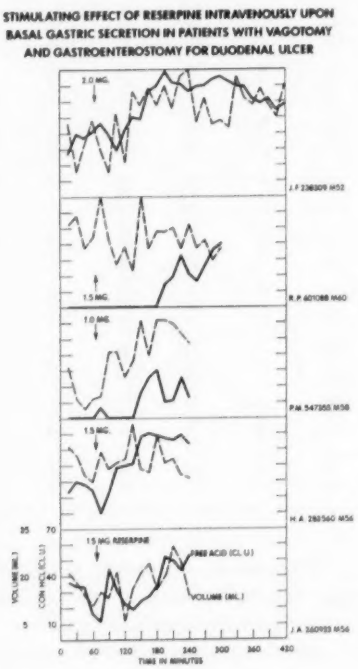


Figure 6

double doses of betazole HCl (Histalog) produced very small amounts of hydrochloric acid three hours later (3 clinical units; 3.5 mg. HCl). In the two patients so studied the intramuscular injection of a potent gastric antisecretory agent (methscopolamine [Pamine], 0.05 mg.) did not demonstrably influence the hypersecretion evoked by reserpine intravenously. According to some observers, methscopolamine lowered the gastric secretory response to a single 0.25 mg. therapeutic dose of reserpine but had no effect upon the action of a single large dose of reserpine;[9,10] these observations are too few for final evaluation.

The blood pressure decreased slightly two to four hours after the intravenous injection of reserpine, persisting to the conclusion of the test. Most patients experienced a generalized sensation of warmth and flushing, continuing usually for approximately one to two hours. In many patients, this flush was accompanied with a vascular type of headache, suggesting clinically the action of histamine or a histamine-like substance. Most persons receiving reserpine intravenously seemed depressed for several hours; this symptom then disappeared completely, with no demonstrable residual manifestations. Eosinophil counts in three patients before and two to four hours after the intravenous administration of reserpine indicated no significant eosinopenia during the tremendous stimulation of gastric secretion.

Comment

The present study demonstrates that reserpine by mouth in standard doses for periods of three months usually does not stimulate gastric secretion significantly in man. The increased outputs of HCl in one

TABLE 5.—*Effect of Single Doses of Hydrocortisone, Corticotropin, and Reserpine Intravenously upon Basal Gastric Secretion in Patients with Duodenal Ulcer*

Patient	Sex	Age	Drug		Basal		Hours Post Drug					
					1st	2d	1st	2d	3d	4th	5th	6th
RH	M	70	Hydrocortisone, 50 mg.	Vol., ml.	44	53	68	28	29	12	18	21
				C.U.	51	70	58	36	11	0	10	38
				Mg.	82	135	143	37	12	0	6	40
			Corticotropin (ACTH), 20 units	Vol., ml.	23	20	45	13	10	16	10	21
				C.U.	21	17	36	29	30	33	31	37
				Mg.	18	12	59	14	11	19	11	28
			Reserpine, 1.5 mg.	Vol., ml.	39	35	27	98	115	120	102	
				C.U.	66	40	32	85	99	100	97	
				Mg.	94	51	31	303	414	437	360	
GM	M	63	Hydrocortisone, 50 mg.	Vol., ml.	39	40	54	63	67	98	72	126
				C.U.	36	55	46	55	64	64	70	90
				Mg.	51	80	90	126	156	228	183	413
			Corticotropin, 20 units	Vol., ml.	83	70	76	67	50	62	55	51
				C.U.	48	40	58	63	52	42	53	68
				Mg.	145	102	160	154	95	95	106	126
			Reserpine, 2.0 mg.	Vol., ml.	68	87	110	140	100	177	167	146
				C.U.	52	60	72	88	78	105	100	102
				Mg.	128	190	288	488	309	676	608	542
WH	M	69	Hydrocortisone, 50 mg.	Vol., ml.	61	36	65	37	57	27	36	46
				C.U.	43	29	43	38	32	22	14	3
				Mg.	95	38	102	51	66	22	18	5
			Corticotropin, 20 units	Vol., ml.	75	38	31	10	20	32	65	55
				C.U.	9	31	14	0	2	26	45	24
				Mg.	25	43	16	0	3	30	106	48
			Reserpine, 1.5 mg.	Vol., ml.	61	64	63	95	100	92	113	126
				C.U.	29	41	51	60	67	63	85	72
				Mg.	64	95	117	207	244	210	350	329
MK (gastric ulcer, duodenal ulcer)	M	75	Hydrocortisone, 50 mg.	Vol., ml.	38	34	18	41	39	39	35	31
				C.U.	24	31	19	6	21	31	6	27
				Mg.	33	38	12	9	30	44	8	31
			Corticotropin, 20 units	Vol., ml.	42	44	28	25	61	39	38	42
				C.U.	14	25	14	13	16	24	44	25
				Mg.	21	40	14	12	36	30	61	38
			Reserpine, 1.5 mg.	Vol., ml.	43	33	42	64	85	84	93	
				C.U.	16	4	5	27	49	45	38	
				Mg.	25	5	8	63	152	138	129	
ET	M	33	Hydrocortisone, 50 mg.	Vol., ml.	61	59	43	17	39	35	78	73
				C.U.	28	24	18	11	27	23	8	27
				Mg.	62	52	28	7	38	29	23	72
			Corticotropin, 20 units	Vol., ml.	91	101	149	62	59	47	105	92
				C.U.	36	37	42	23	22	21	27	49
				Mg.	119	136	228	52	47	36	103	164
			Reserpine, 2.0 mg.	Vol., ml.	120	78	175	255	196	335	248	
				C.U.	41	50	73	95	103	98	107	
				Mg.	179	168	465	882	735	1,195	966	

of eight subjects suggest, however, that occasional persons may be unusually responsive to this compound. Individual variations in responsiveness have been observed with many pharmacologic agents.

The stimulating effect of reserpine intravenously upon gastric secretion is unequivocal and striking. The increases exceeded the responses to such potent stimulants as insulin, histamine, and betazole HCl. The pronounced difference in action of reserpine between oral and intravenous administration is noteworthy, though not unusual; similar trends have been noted with anticholinergic drugs. Presumably, insoluble complexes are formed intraintestinally or the activity of reserpine is lowered in some manner after oral ingestion, permitting absorption of only small proportions of the administered doses. Though this point was not examined directly, larger oral intakes of reserpine might have increased gastric secretion more frequently. The comparative intravenous studies confirmed the tremendous stimulating action of reserpine, in contrast to the negligible effects of hydrocortisone and the negative results with corticotropin. The observations suggest that the gastric effect of

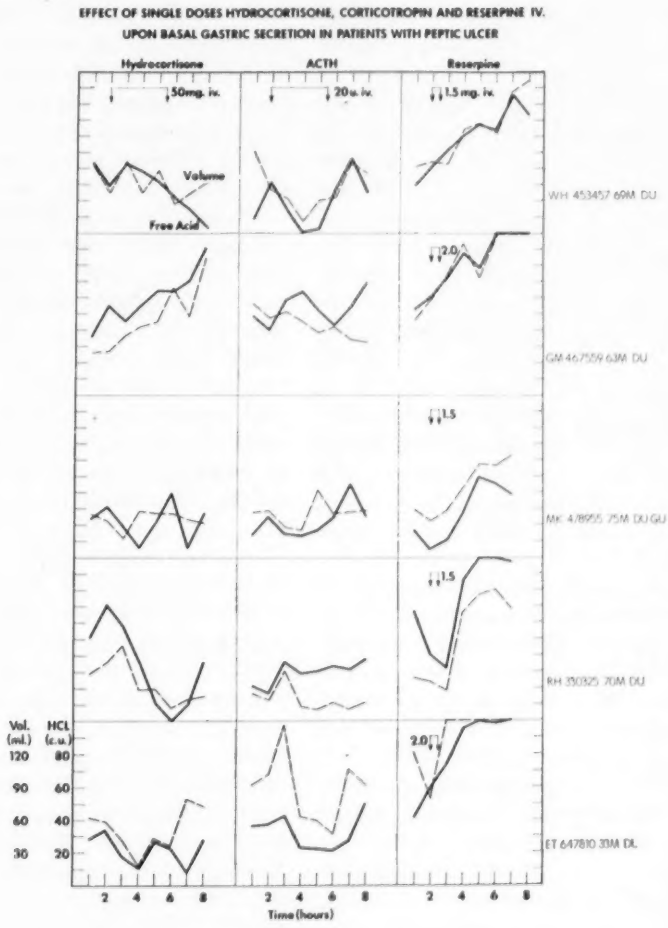


Figure 7

reserpine is not mediated via the adrenal cortex. Some evidence has been adduced in dogs that very large doses (5 mg.) of reserpine may increase adrenocortical activity.[16] The quantities of reserpine in the present study were much smaller and, despite the tremendous increases in gastric secretion, did not cause significant eosinopenia in the patients tested. Preliminary studies by Hammond,[17] indicating that reserpine intravenously stimulated gastric secretion to the same degree in an adrenalectomized dog with a Thomas pouch as in dogs with intact adrenals, also would be in accord with the view that the gastric stimulating effect of reserpine intravenously is not dependent upon adrenocortical function. Reserpine in doses of 1 mg. or more daily by mouth and 4 mg. or more daily by injection did not increase the output of uropepsin.[18]

The mechanism of action of reserpine intravenously is not yet known completely. In general, reserpine lowers blood pressure, slows the cardiac rate, constricts the pupils, causes nasal congestion, increases the appetite, induces a sense of well-being, and exerts a sedative action upon the central nervous system.[19-22] It apparently acts chiefly in the region of the hypothalamus, centrally inhibiting sympathetic influence and correspondingly increasing parasympa-

thetic activity. Large amounts of reserpine have produced signs of Parkinson's disease. Reserpine does not inhibit the effects of epinephrine, arterenol, acetylcholine, or histamine; it does not block transmission in autonomic ganglia, influence the pressure rise induced by stimulation of the efferent vagus nerves, or affect the secretion of pressor amines by the adrenal cortex. The apparent tendency of reserpine to augment parasympathetic activity suggests that its gastric stimulating effect is mediated, in part at least, by the vagal mechanism. On the other hand, the rise in gastric secretion in dogs with vagally denervated (Heidenhain) pouches and the tremendous increases in acid output after reserpine in patients with vagotomy indicate that the peripheral vagal mechanism is not necessary for the stimulating effect.

The pronounced cutaneous flushing and other manifestations of vasodilatation in almost all patients given reserpine intravenously are of considerable interest; other investigators have made the same observation; excessive flushing also has been noted with reserpine given orally in doses of 2 mg. daily.[23] The vasodilatation apparently may be relieved by the intravenous administration of antihistaminics. The peripheral vasodilating effect of reserpine intravenously also has been noted in rabbits; severance of the cervical sympathetic chain abolished the cutaneous vasodilatation, suggesting its mediation, in rabbits at least, via the sympathetic nervous system.[24] Since reserpine is a pure crystalline alkaloid not containing histamine,[25] the possibility arises that reserpine, when given intravenously, releases histamine from intracellular depots. Brodie et al.[26-31] have demonstrated that the action of reserpine involves the liberation of serotonin, a probable neurohumoral agent, from a bound to a free form in brain tissue. The liberation of serotonin persists long after reserpine disappears from the brain, and the free serotonin is regarded as the mediator of prolonged reserpine action. The largest amounts of serotonin are found in the gastrointestinal tract, especially the enterochromaffin cells of the small intestine; other sites include blood platelets and the brain, especially the hypothalamic area. The intravenous injection of reserpine in dogs greatly increased the urinary excretion of the serotonin metabolite, 5-hydroxyindoleacetic acid. According to Benditt and Rowley,[32] both histamine and serotonin are present in mast cells; both compounds are released from mast cells by "histamine liberators" (compound 48/80, dextran, testis extract). Of interest also are the observations that reserpine releases the substance of the enterochromaffin cells in the gastrointestinal tract of rabbits and guinea pigs; it also reduces the histamine content of the rat stomach and causes acute ulceration and hemorrhage in the rat stomach following large doses, such as 5 mg. per kilogram of body weight.[26-31,33] Acute, rapidly healing duodenal ulcers also may be produced in guinea pigs.[34] Perhaps both the vasodilating effect and the tremendous stimulation of gastric secretion by reserpine intravenously are attributable to the endogenous release of histamine; Waalkes and Weissbach[35] have reported release of histamine from rabbit blood by reserpine. Although Benditt and Rowley have not been able to demonstrate that reserpine releases serotonin from mast cells or causes any apparent damage to them, the likelihood also exists that serotonin, liberated from various body depots, may be implicated in the stimulation of gastric secretion and perhaps in the hypersecretion of duodenal ulcer. This intriguing possibility has been under investigation in our laboratory. Since much of the urinary 5-hydroxyindoleacetic acid is derived from serotonin, measurement of the 24-hour output of 5-hydroxyindoleacetic acid is an index of the secretion of serotonin by the tissues in the body. Studies thus far indicate normal outputs of 5-hydroxyindoleacetic acid in the urine of ten patients with duodenal ulcer, suggesting that under ordinary conditions there is no excess serotonin

in the blood and urine of patients with duodenal ulcer. Experimental observations in animals suggest that Dibenamine (N,N-dibenzyl-β-chlorethylamine) and chlorpromazine possesses antiserotonin properties.[36-38] Chlorpromazine also has antihistamine activity. Theoretically, therefore, these compounds might counteract the effects of histamine and serotonin produced endogenously and thereby lower the output of hydrochloric acid. In preliminary studies in our laboratory, chlorpromazine, 25 mg. intramuscularly, reduced the volume of secretion and concentration of acid in two of four patients; the quantities administered may have been too small, though side-effects were pronounced. We have not investigated the possible effect of Dibenamine upon gastric secretion as yet.

The present findings thus suggest that reserpine by mouth, in doses up to 1.0 mg. daily, may be administered with little hazard of stimulating gastric secretion or precipitating the recurrence of peptic ulcer; larger oral doses perhaps should be prescribed cautiously in patients with peptic ulcer. Reserpine intravenously should not be administered to patients with a known or suggestive history of peptic ulcer. The interesting pharmacologic properties of reserpine and its effects upon gastric secretion suggest that reserpine may be a useful tool in further studies of the mechanism of gastric secretion in man.

Summary

Basal gastric acidity increased in one of eight normal persons receiving reserpine, 1.0 mg. by mouth daily for periods of 12 weeks. The most common side-effects were increased appetite, sedation, nasal congestion, and urinary frequency. Reserpine, 1.0 to 2.5 mg. intravenously, increased gastric secretion tremendously in each of four normal persons, five patients with duodenal ulcer, two with benign gastric ulcer, and five patients with duodenal ulcer and vagotomy and gastroenterostomy. Comparative studies of the effects of single doses of hydrocortisone (50 mg.), corticotropin (20 units), and reserpine (1.5 to 2.0 mg.) intravenously upon basal gastric secretion in each of five patients indicated no significant elevation with corticotropin; there was a rise in acid output in one patient and a decrease in another patient given hydrocortisone, and, in contrast, reserpine intravenously stimulated gastric secretion enormously in each case. Practically all patients receiving reserpine intravenously experienced a generalized warmth and flushing, headache, and a sense of depression; the blood pressure decreased slightly to moderately. Eosinophil counts before and during reserpine-gastric hypersecretion did not decrease significantly.

Conclusions

1. Reserpine orally in average quantities (0.25 mg. four times daily for approximately 12 weeks) in normal subjects usually does not increase basal gastric secretion.

2. Reserpine intravenously in doses of 1.0 to 2.5 mg. is a very potent stimulant of basal gastric secretion in man.

3. The tremendous stimulating effect of reserpine intravenously upon gastric secretion apparently is not dependent upon an intact vagal mechanism or upon adrenocortical stimulation.

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Movements and Forces of the Human Heart

I. The Genesis of the Apical Impulses

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Introduction

The present study is the first of a series concerning the circulatory forces responsible for the motions of the heart and of the body in health and in disease. Ideally, such investigations should deal first with the normal motions in order that limits may be established for the recognition of abnormalities. However, the normal motions are complex, and in some instances their interpretation is facilitated by the simultaneous study of certain abnormal states. In the first several publications in this series, the movements, as observed in normal subjects, will be emphasized, and abnormal conditions will be considered only in so far as they may aid in understanding the findings in the normal persons.

The movements of the heart as reflected in tracings from the precordium are numerous and complex. Only one such movement is ordinarily detectable by physical examination. This is, of course, the apex beat. Hence this movement has been chosen as the first one to be investigated in detail in the present series of reports. It is interesting to note that William Harvey was apparently the first to recognize that the apex beat is a systolic phenomenon. Prior to his publication of "De Motu Cordis," it had been generally assumed that this movement was the result of filling of the heart and occurred in diastole.

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Methods

The subjects studied consisted of a group of healthy men, most of whom were in the third decade. Six patients with bundle-branch block (three left and three right), who had no evidence of clinically significant heart disease, were also investigated. The studies on these patients will be reported in detail later, and only such aspects of the findings as are applicable to the problem of the genesis of the normal apex beat will be mentioned in the present report. Tracings from a few patients with various types of cardiac disease will be presented, but only insofar as they appear to be relevant to the general problem of the mechanism of the normal apex beat.

Precordial movements (kinetocardiograms) were registered by means of a small bellows, as previously described.[1-3] In some instances the bellows was attached to a fixed point outside the chest, while in other instances it was attached to a funnel strapped to the chest. The records obtained by the two techniques were identical in most respects, but the latter method offered the advantage of making it possible to obtain records during respiratory maneuvers. When the bellows was attached to a fixed point away from the chest, the thoracic movement of respiration were so large in relation to the circulatory precordial movements as to make it impossible to obtain satisfactory records.

Tracings were obtained routinely from the right and left parasternal regions (K_1 and K_3 points, respectively), and from the region of the apex (K_4 point). Records were made with the breath held at the end of normal expiration and also during the Müller and Valsalva maneuvers.

In some subjects records were obtained from the right (KER) and the left (KEL) portions of the epigastrium from the left axilla (K_6 point).

As reference tracings the electrocardiogram, carotid pulse, and heart sounds were utilized. Ballistocardiographic (BCG) tracings were likewise made in most instances. However, during the four years of the study the BCG technique was modified in several respects in an attempt to eliminate artifacts and to secure tracings of greater fidelity in relation to circulatory forces.

Since these ballistocardiographic investigations are still in progress, the data concerning the BCG in relation to the apex beat and to other circulatory forces are not included in the present study and will be reported in subsequent communications.

Results

The findings may be conveniently divided into two groups, of which the first deals with the apex impulse in subjects with normal hearts and the second with the findings in patients with various disorders associated with exaggeration of the apex beat.

The Normal Apex Impulse.—The normal impulse is a gentle tap. It begins about 0.07 to 0.08 second after the start of the QRS complex of the electrocardiogram and lasts for about 0.05 second, terminating at approximately the time of the beginning of the carotid upstroke. In many normal subjects it can be seen that the impulse is biphasic (Fig. 1*A*, arrow).

The first phase of the normal apex beat is frequently associated with a rightward-forward-footward movement (upstroke) in the right epigastrium, but not in the left epigastrium (Fig. 2). This initial portion of the apex beat (arrow) persists during the Müller procedure but is decreased or absent during the Valsalva procedure (Fig. 1, *B* and *C*). The initial phase of the apex beat (arrow) is delayed in patients with right bundle-branch block (Fig. 3).

These findings indicate that the initial portion of the apex beat, i. e., that portion starting at 0.07 to 0.08 second after the electrical excitation and ending 0.10 to 0.11 second after excitation, is of right ventricular origin. The movements are abrupt, and they occur at a time corresponding to the onset of the rise in pressure in the pulmonary artery, as found by Coblenz et al. and Braunwald et al.[4,5] It therefore seems likely that recoil consequent to right ventricular ejection is occurring at this time and that such recoil pushes the apex forward and initiates the apex thrust.

The second phase of the normal apex beat begins about 0.10 second after the

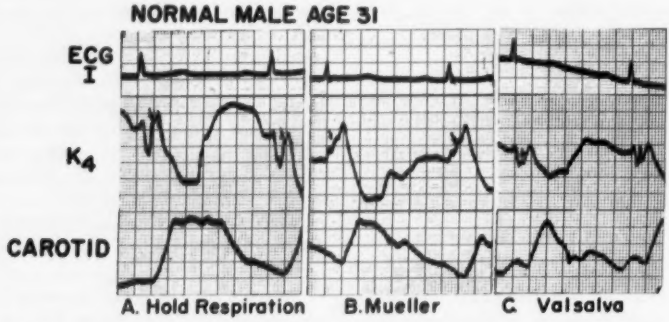

Fig. 1.—A typical precordial trace taken at the region of maximal apex impulse, in this instance at the K_4 point which corresponds to the V_4 point of the electrocardiographic lead. The trace was taken at a paper speed of 50 mm. per second, so that each vertical line represents a time interval of 0.02 second. Lead I of the electrocardiogram was simultaneously recorded for reference. Trace *A* in the left-hand figure was taken with respiration held at the point of normal expiration. The apex thrust is the first major abrupt outward movement after the onset of the QRS complex in the ECG. The arrow in Trace *A* indicates the point at which the slope of the apex impulse abruptly changes, indicating there are at least two components in the normal apex thrust. In Trace *B* (taken during the Müller maneuver), the arrow points to the initial phase of the apex thrust which persists, while in Trace *C* (during the Valsalva maneuver) the initial part is essentially absent or diminished, as indicated by the arrow. Note that in this instance the initial part of the apex thrust is represented by a flat portion in the trace. The second portion is accentuated during the Valsalva maneuver and corresponds in time to the onset of the second portion of the apex thrust, as noted in the trace taken during held respiration.

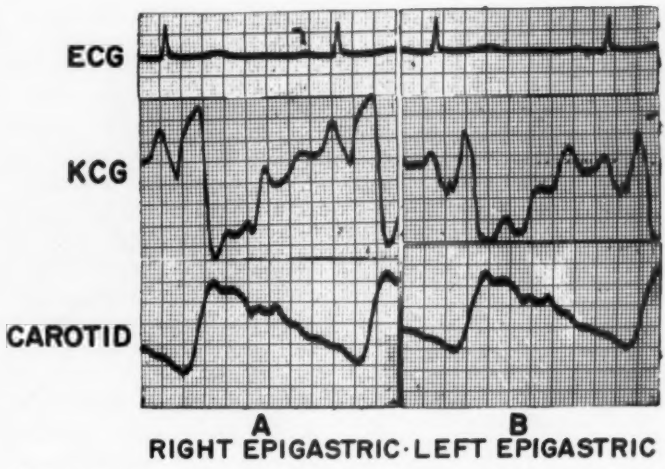

Fig. 2.—Typical traces taken from the right and left epigastric regions just below the costal margin in the midclavicular line. The trace was recorded with a paper speed of 50 mm. per second, so that each vertical line represents a time interval of 0.02 second. Note that the prominent outward movement in the right trace approximately 0.08 second after the onset of the QRS complex corresponds in time to the initial phase of the apex thrust. This initial movement is essentially absent when the tracing is taken from the left epigastrium, as noted in Trace *B*. The major outward movement in the left trace begins approximately 0.10 second after the onset of the QRS complex, and corresponds in time to the second portion of the apex thrust, as noted in Figure 1.

onset of excitation in the electrocardiogram and about 0.01 to 0.02 second before the beginning of the carotid upstroke. At this time there is usually a sharp outward movement in the left epigastrium (Fig. 2*B*) which follows the movement previously mentioned in the right epigastrium. Likewise, there is frequently an outward movement in the left axilla at the K_6 point (arrow, Fig. 4). This second portion of the apex thrust is diminished during the Müller procedure, but persists and may be exaggerated during the Valsalva procedure (Fig. 1). In patients with left bundle-branch block the initial phase of the apex thrust is not delayed, but the second phase is delayed (Fig. 3). These several points lead to the conclusion that the second phase of the apex thrust is of left ventricular origin. Before considering its genesis in more detail, it may be well to analyze the apex thrust in certain abnormal conditions.

The Exaggerated Apex Impulse.—Exaggerations of the apex thrust occur in a number of conditions. While left ventricular hypertrophy is frequently a common denominator and probably the most common cause for an exaggerated impulse, there are certain basic differences in the pattern of the apex impulse which depend on the etiologic factors as well as differences in the hemodynamics. Thus the exaggerated apex impulses will be subdivided further.

Left Ventricular Hypertrophy Due to Outflow Pressure Loads.—Patients with hypertension or well-marked aortic stenosis frequently display an impulse which is slightly further to the left than normal, which occupies a somewhat greater area, and which is definitely heaving, lifting, and expansile in nature, in contrast to the gentle tap of the normal apex impulse. The records show that the apex thrust begins at approximately the time of the normal impulse (occasionally they may begin earlier—the reason for this not being apparent at this time), but it is exaggerated in amplitude and in duration, lasting throughout most of systole (Fig. 5*A*). In addition, the

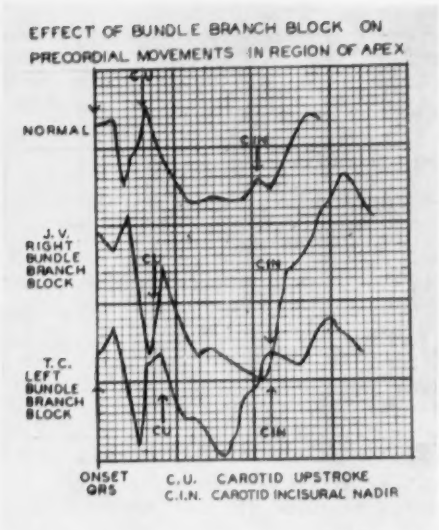

Fig. 3.—The apical traces in two subjects with bundle-branch block and in a normal person are depicted. In both of these subjects the bundle-branch was idiopathic and not associated with any detectable heart disease. The onset of the QRS complex, the beginning of the upstroke in the carotid pulse trace (*CU*), and the carotid incisural notch (*CIN*) are indicated. The vertical lines represent a time interval of 0.02 second. The initial phase of the apex thrust occurs approximately 0.12 second after the onset of the QRS complex in the patient with right bundle-branch block. In the patient with left bundle-branch block, the initial phase of the apex thrust begins 0.10 second after the onset of the QRS complex of the electrocardiogram. In normal subjects this event occurs 0.085 ± 0.015 second after the beginning of excitation.

normal inward movement, which ordinarily precedes the outward movement of the apex thrust, is usually absent in these patients.

Aortic Insufficiency.—The apex impulse in patients with aortic insufficiency is usually similarly exaggerated in amplitude.[6] However, there are two important differences which are noted in patients with marked functional impairment: (1) The impulse begins earlier than normal (i. e., about 0.04 second after the onset of the QRS complex in the electrocardiogram); (2) instead of being sustained throughout the entire period of ejection, the impulse ends abruptly about the time of the onset of ejection, and there is a well-marked retraction during mid and late systole (Fig. 6). Thus the impulse can easily be noted at the bedside to be very abrupt and terminate very quickly and to lack the sustained thrust as usually noted in patients with hypertension or aortic stenosis.

Myocardial Infarction in Region of the Apex.—Myocardial infarction in the region of the apex tends to produce a characteristic impulse. Simple palpation reveals that the apex thrust is even more forceful and more widespread than those just previously discussed and is likely to have a longer duration than those noted in hypertension or aortic insufficiency. Traces from the point of maximal apex thrust indicate that the impulse begins much sooner after the onset of ventricular excitation and much longer before the upstroke of the carotid pulse than that usually noted in the case of the normal impulse or the apex thrust of hypertension or of aortic stenosis. The characteristic trace is illustrated in Figure 5*B*. Indeed, the diagnosis of infarction can frequently be made by simple palpation, as no other condition causes an apex thrust occupying such a large area and having such a long duration.

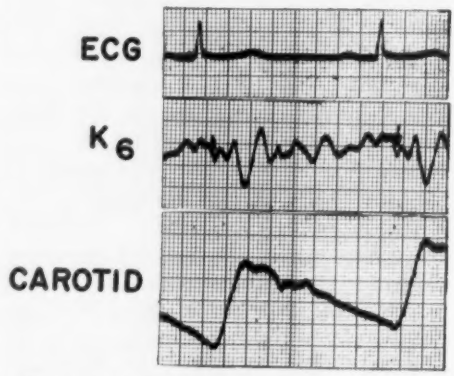

Fig. 4.—A trace taken from the K_6 point, which corresponds to the V_6 point of the precordial electrocardiographic lead. Notice that at approximately 0.10 second there is an outward movement. This corresponds in time to the second part of the apex thrust as seen in Figure 1*A*. At 0.08 second, the time of onset of the first portion of the apex thrust (Fig. 1*A*), there is an inward movement in the K_6 position, above. The trace was recorded with a paper speed of 50 mm. per second, so that each vertical line represents a time interval of 0.02 second.

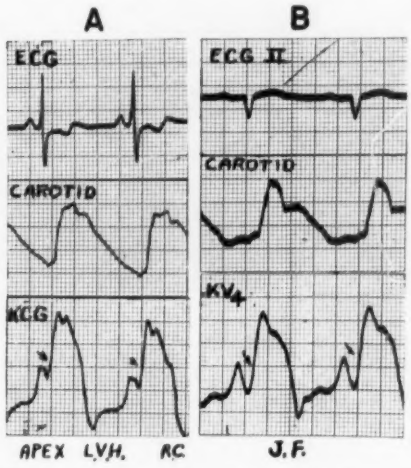

Fig. 5.—These tracings were taken from the point of maximal apex impulse (*A*) in a patient with hypertension and left ventricular hypertrophy, and from the corresponding point in another patient (*B*), in which where was an anterior septal myocardial infarction. The trace was recorded during held respiration, with a paper speed of 25 mm. per second, so that each vertical line represents a time interval of 0.04 second. The apex impulse is indicated by the arrow. The outward and then inward movement just preceding the apex thrust begins during the P wave before the QRS complex and is presumed to be due to auricular activity. Note that the apex thrust in Tracing *A* begins 0.08 second after the onset of the QRS complex, while in the trace from the comparable point in the patient with an anterior septal myocardial infarction, the apex impulse as indicated by the arrow begins approximately 0.04 second after the onset of the QRS complex.

The apex thrust is of special interest in certain patients with angina pectoris. These subjects may display, during an attack of pain, a well-marked apical bulge resembling that seen in patients who have had an infarction in the region of the apex. Of special interest is the observation that glyceryl trinitrate in either the form of tablets, sublingually, or the form of long-acting glyceryl trinitrate ointment may reverse such an apical bulge or prevent it. These observations are illustrated in Figure 7.

All patients with angina pectoris do not show such changes in the character of the apex thrust. These changes are possibly limited to persons in whom the area of ischemia is in the apical region. However, when a bulge limited to this region does occur, it can frequently be predicted that the electrocardiogram will display the maximal changes in the V_4 and V_5 regions. The "anginal bulge" usually begins in midsystole when the intraventricular pressure is highest, while the "infarctional bulge" begins much earlier, as intraventricular pressure begins to rise.

Apex Thrust in Mitral Insufficiency.—The apex thrust in patients with "pure" mitral insufficiency is usually not exaggerated to the degree noted in other conditions just presented. It begins somewhat later and reaches its point of maximal outward movement approximately at the carotid incisural notch (Fig. 7). Thus on palpation of the impulse in this group of patients, the delayed apex thrust can often be detected at the bedside if one is careful to time the movements in relation to the heart sounds or to the carotid pulse.

Other Causes.—There are at least two other conditions which may be associated with a prominent apex thrust. One of these is the group of disorders accompanied by a well-marked elevation in the cardiac output. In these states the increased promi-

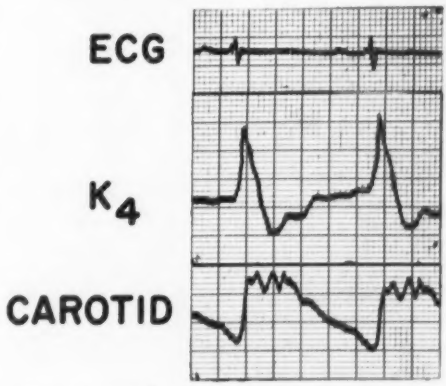

Fig. 6.—Tracing taken from the point of maximal apex impulse, or in this instance the K_4 point which corresponds to the V_4 position in the electrocardiographic precordial leads, from a patient with aortic insufficiency. Note that the apex impulse is a very abrupt outward movement beginning very early after the onset of the QRS complex or, in this instance, 0.04 second and terminates abruptly shortly after the onset of ejection is noted from the carotid trace. Note that the impulse is very abrupt and of short duration, followed by retraction during most of the ejection period.

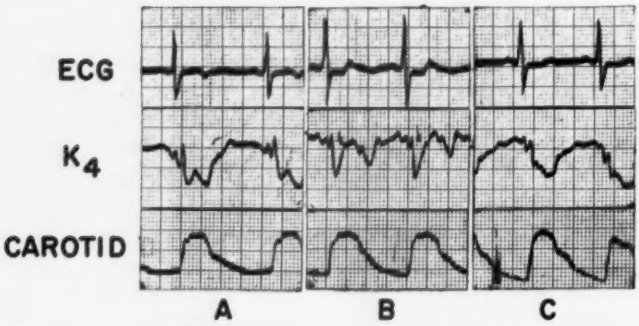

Fig. 7.—*A*, *B*, and *C* are traces taken from the K_4 point in a patient with angina pectoris. In Trace *A*, the control, note that during the major portion of ejection there is a well-defined inward movement of retraction of the apical region of the chest at this point, which is similar to that usually noted in normal subjects. Trace *B* is taken after exercise, during which patient experienced typical substernal pain associated with S-T segment shifts, as noted in the ECG (Lead II). Note that instead of the sustained retraction during ejection, as is noted in the control trace, there is now a bulge present during mid and late systole as indicated by the arrow, which suggests that during the myocardial ischemia associated with the anginal pain the patient developed a ventricular aneurysm at this point. Trace *C* was taken following glyceryl trinitrate and the same amount of exercise which produced the pain in Trace *B*. In this instance the patient did not experience any pain and developed no bulge (arrow in *B*). Thus glyceryl trinitrate not only was apparently able to prevent the onset of symptoms following standard exercise, but in this instance prevented an aneurysmal bulge in the apical region of the heart as well.

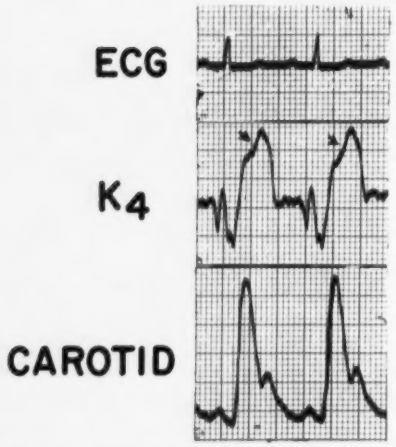

Fig. 8.—Traces taken from the point of maximal apex impulse from the K_4 point in a patient with "pure" mitral insufficiency. The Lead II of the ECG is used as a reference trace. Note that the apex thrust, or first major outward movement after the onset of the QRS complex, begins approximately at the normal time, or 0.08 second after the onset of the QRS complex. However, it is sustained, and there is a marked increase in amplitude during mid and late systole, reaching a peak just before the incisural notch in the carotid pulse tracing.

nence of the apex beat is associated with exaggeration of the pulsations of the entire precordial area, and usually with increased intensity of the heart sounds and a full bounding pseudo-Corrigan pulse. An unusually prominent apex thrust is also observed in certain patients with right ventricular hypertrophy. In these instances there is usually a heaving, forward movement of the entire precordium, and it would appear that this movement, as well as the exaggerated apex thrust, is due to the thickened right ventricle, which not only extends anteriorly over the precordium but reaches over the left margin of the heart and makes up the apical region (Fig. 9). A distinction between the latter two groups of conditions, i. e., disorders associated with an increased cardiac output and forms of heart disease accompanied by right ventricular hypertrophy, is usually not difficult clinically. Both conditions tend to be associated with pronounced heaves of the entire left precordial area, with exaggeration of the apex thrust. However, patients

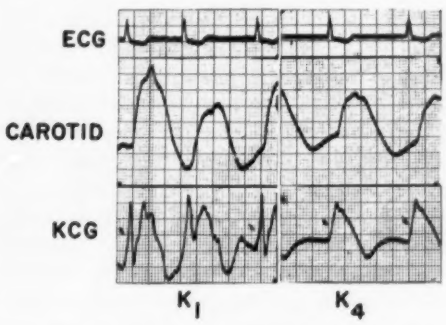

Fig. 9.—Trace taken from the K_1 and K_4 points (corresponding to the V_1 and V_4 points of the precordial electrocardiographic V leads), on a patient with mitral stenosis. Note that abruptly about 0.04 second after the onset of the QRS complex in both instances there is a large well-defined outward movement, indicated by an arrow in both traces. Thus apparently the apex thrust which is seen in the K_4 trace is apparently the same movement which is present over the entire precordium and is thought to be due to the thickening of the right ventricle, which extends anteriorly over the precordium to make up the left margin of the heart and the apical region.

with increased cardiac output usually have a full, bounding pulse, and, in addition, the lower parasternal region of the chest can usually be seen to retract well during systole. In contrast, those with right ventricular hypertrophy have in most instances a normal or small pulse volume, and the lower parasternal region of the chest is sustained out during the entire ejection period, thus producing a much more sustained heave than that noted in conditions associated with increased cardiac output.

Comment

Evidence has already been cited for the conclusion that the normal apex beat is ordinarily initiated by recoil consequent to right ventricular ejection. There is strong evidence that this chamber ejects about 0.07 to 0.08 second after the onset of the QRS complex.[4,5] The observation that there is a forward movement of the right side of the epigastrium but not of the left is strongly in favor of the concept that right ventricular recoil is occurring at this time. Similarly, the findings that this initial portion of the apex beat is delayed in patients with right bundle-branch block but not in those with left and that this movement is exaggerated during the Müller maneuver but decreases during the Valsalva procedure are, likewise, in keeping with the idea that right ventricular recoil is responsible for the initiation of the normal apex beat. At about 0.08 second after the onset of excitation, a footward force is registered by the force ballistocardiogram (start of H-I downstroke), and electrokymograms of the aortic arch usually display footward motion (Fig. 10). This finding suggests that the aortic annulus is being pulled downward, and such a movement might cause a forward-footward push on the apex.

The latter portion of the apex thrust in normal subjects appears to be of left ventricular origin and may be related to left ventricular recoil. The findings that the last portion of the apex beat tends to be increased by the Valsalva procedure and that it is delayed in patients with left bundle-branch block point strongly toward the left ventricle as responsible for this portion of

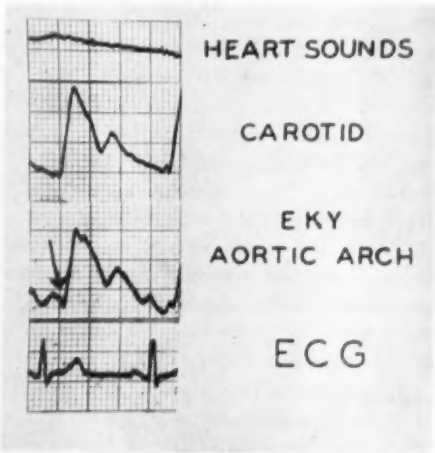

Fig. 10.—An electrokymographic trace of arch of the aorta with a slit—vertical so that the motion of the arch of the aorta is recorded in a headward-footward direction. Note the footward movement in the trace, which occurs 0.08 second after the onset of the QRS complex and precedes the marked outward movement. This suggests that the aortic arch is being pulled footward at this time, possibly as a manifestation of the forward footward push on the apex to produce the apex thrust.

the apex thrust. The close association of this movement with outward motion in the region of the left epigastrium and in the left axilla constitutes evidence for left ventricular recoil as the factor responsible for the terminal portion of the apex thrust.

On the other hand, it does not seem likely that left ventricular recoil is responsible for the exaggerated apex thrust noted in abnormal states. The recoil movement in normal subjects is of brief duration, while the apex thrust in patients with left ventricular hypertrophy, and particularly in those with postinfarctional aneurysms in the region of the apex, has long duration. Likewise, the latter conditions are associated with an actual expansile pulsation, which is not noted in normal subjects. It would appear that the exaggerated apex thrust observed in these several conditions is related to a disproportion between the strength of the apical and of the basal musculature of the left ventricle. Such disproportion might occur either (1) because there is hypertrophy of the entire left ventrical with the stronger and thicker base being more hypertrophied than the thinner apex, or (2) because there is actual weakening due to ischemia of the muscles in the region of the apex. In either case the more forcible contraction of the basilar muscles (either relative or actual) will tend to cause ballooning of the thinner-walled apex. Thus it would appear that in the case of patients with exaggeration of the apex thrust the impulse is not related to left ventricular recoil alone, but, more particularly, to an aneurysmal dilatation of the apex consequent to the contraction of the basilar musculature of the left ventricle.

The question arises as to whether this aneurysmal ballooning mechanism is concerned in the production of the terminal portion of the normal apex impulse. The techniques used in the present study do not allow any absolute answer to this question. However, the close association of the terminal portion of the apex impulse, with sharp and brief outward movement in the left part of the epigastrium and in the left axilla, points more strongly toward left ventricular recoil. In any case, the findings during the Müller and Valsalva maneuvers in normal subjects and the observations in patients with bundle-branch block but without evidence of clinically significant heart disease indicate clearly that the latter part of the apex beat is of left ventricular origin, while the initial portion is of right ventricular origin.

It may be pointed out that a great deal may be learned by simple palpation and that this method is often more informative than either the x-ray or the electrocardiogram. Indeed, we have records of a patient who displayed a well-marked bulge of the apex during an anginal attack and yet had no electrocardiographic change in the trace recorded from the same precordial area. This apparently paradoxical finding can be explained by the observations of Massumi et al.,[8] who have demonstrated that the outer portion of the myocardium is responsible for the electrocardiographic tracing as recorded. Presumably, a person displaying an apical bulge during an anginal attack, and yet a normal electrocardiogram, has temporary ischemia of the subendocardial musculature with little or no ischemia of the subepicardial portion.

An apex impulse which has the normal tapping character but is to the left of the normal position is likely to be due to either displacement or dilatation. Physical examination of the lungs will usually enable one to make this distinction at the bedside. The conditions which cause cardiac displacement of a significant degree are likely to be associated with well-marked abnormalities of the pleural cavities.

When an unusually forceful apical impulse is encountered with increased pulsation over a greater than normal area, a number of possibilities arise. If the patient has a well-marked increase in the precordial movement, generally, there are at least four possible causes. There may be increased cardiac output, which can be readily detected in most instances by the presence of

a bounding full pulse and an increased pulse pressure. If there is extreme right ventricular hypertrophy to account for the precordial heave and increased apical thrust, the pulse volume will be normal or small in most instances, and the pulse pressure will not be increased. A third possibility is hypertrophy of both ventricles, and a fourth is infarction (or ischemia) involving both the apex and the interventricular septum.

When there is exaggeration of the apical thrust without any associated increase in the motions in the left parasternal region, a different group of possibilities should be considered. If the apex is confined to a region the size of half a dollar or less but is well-sustained and definitely expansile, it is likely that one is dealing with left ventricular hypertrophy. If, on the other hand, the impulse is felt over a considerably wider area (that occupied by a silver dollar, or more) the possibility of apical ischemia should be considered. If such ischemia is the result of an anginal attack, it is likely that the exaggerated impulse will disappear following the administration of glyceryl trinitrate. However, if there is extensive infarction of the apex, the exaggerated impulse persists despite such therapy, and precordial tracings will reveal that it begins very early in isometric systole.

Summary

The normal apex impulse may be divided into two parts. The first of these, which begins about 0.08 second after the beginning of electrical excitation, is believed to be related to recoil as the right ventricle ejects. This portion of the apex beat is associated with sharp outward movement of the right portion of the epigastrium, is exaggerated by the Müller maneuver, and is delayed in persons with right bundle-branch block but not in those with left.

The second portion of the apex beat begins about 0.11 second after the onset of electrical excitation and about 0.01 second before the beginning of the carotid upstroke. This portion of the apex thrust is believed to be of left ventricular origin. It is diminished by the Müller maneuver and may be increased by the Valsalva procedure. Since this second portion of the apex thrust is accompanied by sharp outward movements in the left epigastric region and in the left axilla, it is believed that recoil as the left ventricle ejects is a factor in its production.

Various conditions which may cause exaggeration of the apex thrust have been studied. It is concluded that most such conditions (aneurysm of the left ventricle, anginal attacks with ischemia of the apex, and left ventricular hypertrophy) are associated with a disproportion between the strength of the muscles at the base and at the apex of the left ventricle, respectively. The result is an aneurysmal bulge of the apex of the left ventricle due to the more forcible contraction of the stronger muscles at the base.

The possibility that such an aneurysmal bulge may exist in smaller degrees in normal subjects and may contribute somewhat to the genesis of the normal apex beat cannot be excluded on the basis of the present evidence.

Certain points are cited which will frequently enable the observer at the bedside to distinguish between the various causes of exaggerated apex thrust without the aid of instrumental methods.

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Alveolar Carbon Dioxide Measurements in Normal and Emphysematous Subjects

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Chronic pulmonary disease, particularly emphysema, presents a problem in a hospital treating males of the older age group. Pulmonary emphysema may be encountered as a complication of any disease, but in spite of its high incidence, little is known concerning its basic abnormal physiology. The importance of carbon dioxide in the control of respiration was first considered by Miescher-Rush, cited by Best and Taylor,[1] in 1885, and amplified by Haldane and Priestley,[2] who pointed out the importance of the blood pCO_2 as one of the controlling factors. Scott[3] related the ventilatory response of his subjects to the inhalation of CO_2 in varying concentrations in view of the emphysematous patient's increased tolerance to a high alveolar CO_2 concentration. He concluded that the diminished response in the emphysematous persons as compared with the normal was due to the increased buffering capacity of the body fluids. Donald and Christie[4] expanded Scott's work and demonstrated a decreased response to the inhalation of 4% CO_2 in 75% of their emphysematous patients but concluded that an explanation based only on the blood buffer theory or variation in the sensitivity of the respiratory center was not adequate. These observations led later investigators to use CO_2 in oxygen as the inspired gas to eliminate hypoxia and to relate the diminished ventilatory response in the emphysematous person to both the resting CO_2 retention and to the arterial pCO_2. This paper presents a preliminary report of studies of a group of normal persons and a selected group of emphysematous patients whose ventilatory response and alveolar pCO_2 values were determined under a number of varying conditions.

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Methods

The age of the emphysematous patients ranged from 25 to 69 years. They were carefully selected, free of concomitant upper respiratory infection, congestive heart failure, and other complicating physical or emotional conditions. After chest fluoroscopy and a physical examination, they were instructed regarding the purposes of the procedure to be done. The ages of the normal group ranged from 26 to 64 years and included hospital patients as well as employees without respiratory disease.

Inspiratory gases, compressed air, oxygen, or carbon dioxide-oxygen mixtures were supplied through a manifold-demand valve arrangement. The subject was so positioned that he could not know the composition of the inhaled gas or the moment of transition from one gas mixture to another. Basic lung volume measurements were accomplished with the subjects in the sitting-resting position, using a Collins 9 liter spirometer. The maximum ventilatory volume (MVV) (20 seconds) and the resting minute volume measurements were done in the usual manner using a 120 liter Tissot spirometer.

A maximum expiratory alveolar CO_2 and a resting average expiratory CO_2 concentration were recorded, using a Liston-Becker infrared carbon dioxide analyzer incorporated as part of the respiratory circuit. The analyzer was connected to an Esterline-Angus strip chart recorder using a chart speed of either 0.5 cm. per second or 30 cm. per minute. During the procedure, frequent

calibration checks of the CO_2 analyzer were made. No correction was made for moisture content of the gas. Expiratory gas was passed directly through the detector unit for alveolar CO_2 concentration measurement, or it was bypassed around the detector unit by means of a valve arrangement. When the detector was bypassed, a small aliquot of the respiratory gas was continually aspirated through the detector unit to record the average expiratory CO_2 concentrations. This averaging method is not absolutely accurate, since the length of the expiratory period would influence the indicated average, but for group comparison the relative CO_2 concentrations were considered valid.

During the MVV test, the carbon dioxide concentration of each respiration was recorded, and immediately following the last expiration of the 20-second period a sample of alveolar gas was obtained for measurement. An aliquot of the total expired MVV test gas was then analyzed for the CO_2 concentration.

After a brief rest, minute volume studies, average expired CO_2, and alveolar CO_2 concentrations were recorded for periods of at least three to five minutes each, while the subject breathed oxygen, compressed air, 2.5% CO_2-97.5% O_2, or 7.5% CO_2-92.5% O_2. Measurements of alveolar pCO_2 were made precisely at the completion of the breathing of each of the gas mixtures.

All gas volume measurements were corrected to BTPS. The calculations of predicted values for some of the measured functions were made using Baldwin's formulae,[6] taking into account age, weight, and body surface area. Timed (three second) vital capacity measurements were calculated as the per cent of measured total lung volumes rather than the per cent of predicted lung volumes. A statistical analysis of the results was made according to the nonpaired method, and the null hypothesis was rejected at the 2% level.

Results

A summarization of the data and statistical analysis is presented in the Table. A comparison of the minute volumes measured during a period on air showed a slightly smaller volume for the patients with emphysema, but this difference was not considered to be significant ($t=0.05$). When 100% oxygen was used for the inspired gas, the difference between the minute volumes of the two groups was even less significant. In each of the groups, however, the mean minute volume on oxygen was slightly lower than the mean minute volume while breathing air. The three-second and total vital capacity measurements and the MVV test indicated a highly significant difference between the two groups. The inhalation of 100% oxygen resulted in a lowering of the mean alveolar CO_2 in both groups as compared with the same determination on air. The resting average carbon dioxide concentration was also somewhat lower when each group was breathing 100% oxygen. This was not the expected result, since some investigators have shown oxygen to stimulate the minute volume in normal persons and to

Summarization of Data

	Normal Subjects, N=20		Emphysematous Subjects, N=22	
	Mean	S. D.	Mean	S.D.
Vital capacity, per cent of predicted	96.7	8.0	69.1*	15.6
3-second vital capacity, per cent of total	97.3	4.3	75.0*	14.3
Maximum ventilatory volume, per cent predicted	81.3	14.8	34.7*	10.3
Maximum ventilatory volume, l./min.	99.00	19.1	33.77*	12.04
Minute volume (100% O_2), l./min.	11.79	2.52	10.40	2.69
Minute volume (air), l./min.	11.83	2.61	10.51	1.48
Maximum minute volume (2.5% CO_2-97.5% O_2), l./min.	16.82	2.59	13.33*	2.60
Maximum minute volume (7.5% CO_2-92.5% O_2), l./min.	32.11	8.74	20.94*	5.57
Maximum minute volume (2.5% CO_2) / Minute volume (O_2)	1.47	0.93	1.31	0.23
Maximum minute volume (7.5% CO_2) / Minute volume (O_2)	2.78	0.55	2.07	0.59
	pCO_2†		pCO_2†	
Alveolar CO_2 (resting), per cent	5.02 (35.4)	0.91	5.90* (41.6)	1.01
Alveolar CO_2 (post-MVV), per cent	3.66 (25.8)	0.74	5.05* (35.6)	1.31
Alveolar CO_2 (100% O_2), per cent	4.36 (30.74)	0.95	5.26* (37.0)	1.05
Alveolar CO_2 (2.5% CO_2), per cent	5.33 (37.58)	0.57	6.33* (44.63)	0.84
Alveolar CO_2 (7.5% CO_2), per cent	7.76 (54.71)	0.22	8.18* (57.67)	1.42
Resting average CO_2 (air), per cent	4.09	0.85	5.35*	0.37
Resting average CO_2 (100% O_2), per cent	3.42	0.59	2.91*	0.43
CO_2 eliminated during MVV, ml./min.	465.9	118.0	349.9*	71.4

* Significantly different from normal subjects at 2% level or better.
† Millimeters of Hg.

have a depressing effect in those with emphysema.

When carbon dioxide in oxygen was used as the inhaled gas and the mean of the maximum minute volumes was used as the basis for comparison, the difference between the two groups was highly significant. Although both groups responded to increased CO_2 in the inhaled gas, the response of the normal was much more marked, as is evidenced by the nearly threefold increase in the minute volume of the normal group as compared to the doubling in the emphysema group. The relative stimulating effect (percentage increase) of the two concentrations of carbon dioxide on the two groups is demonstrated by the ratios in the Table. It was noted that an intergroup comparison demonstrated no significant difference when the lower percentage of CO_2 was breathed. In contrast, employment of the higher concentration of CO_2 resulted in a clear separation of the two groups.

The influence of inhaled carbon dioxide in the two groups is shown in the bar graph (Fig. 1) and by the average concentration of carbon dioxide expired under the conditions noted (Table). An important group difference is indicated by the higher alveolar CO_2 concentration in the emphysema group during each of the test periods. In spite of this higher alveolar pCO_2, the average carbon dioxide concentration in the expired gas was lower in the emphysema group (Table). The group difference was further emphasized by the lowering during the 20-second MVV test of the alveolar pCO_2 (6.0 mm.) in the disease group as compared with the more significant decrease (9.6 mm.) in the normals. The volume of CO_2 actually eliminated during the MVV test was considerably less in the emphysematous group than in the normal group.

The resting alveolar pCO_2 of the individuals within each group related to the respective MVV test is shown as a scattergram (Fig. 2). When resting alveolar pCO_2 levels were compared with the individual maximum minute volumes following stimulation with the higher percentage of carbon dioxide, a similar relationship was observed.

The use of the 7.5% CO_2 as the test gas resulted in an elevation of the mean alveolar pCO_2 of the normal group to approximately the same concentration as that of the carbon dioxide being inhaled, whereas in the emphysematous subjects the mean alveolar carbon dioxide concentration was considerably higher than the carbon dioxide concentration inhaled. There was a greater variation in the expired alveolar pCO_2 in

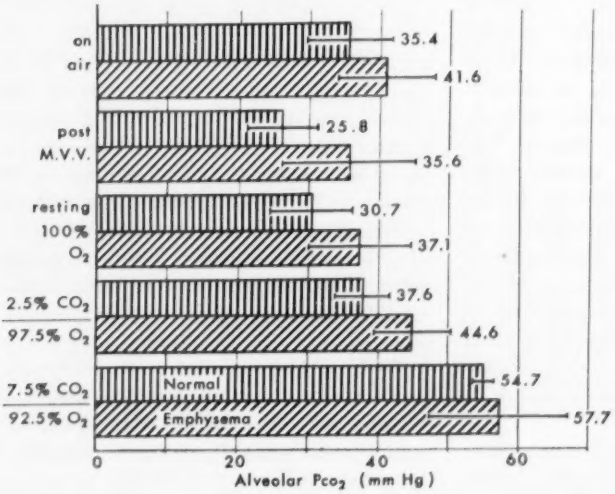

Fig. 1.—Alveolar pCO_2 values measured in the normal and emphysema groups during the test periods.

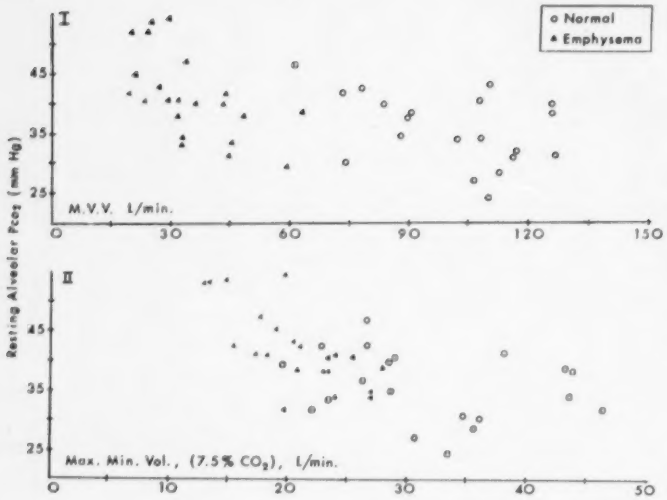

Fig. 2.—Scattergram showing relationship of alveolar pCO_2 to the maximum ventilatory volume (based on a 20-second measurement) and to the maximum minute volume response to 7.5% CO_2.

the emphysematous persons. Some of the more severely emphysematous patients were observed to have an alveolar pCO_2 as high as 70.5 mm. Hg.

Comment

Considerable difficulty is experienced in evaluating the relative degree of impairment seen in patients with diagnoses of emphysema. By better utilization of present diagnostic methods in the roentgenologic and pulmonary function laboratories, an earlier correlation with the clinical picture could be achieved and a better understanding of early pulmonary emphysema established. Early accurate diagnoses would aid in the development of measures directed toward the alteration of the course of the disease. The emphysema group and the normal group were well differentiated statistically by the timed vital capacity test (three seconds) and the MVV test, reflecting the fixation of the thoracic cage and the inelasticity of the lung tissue. Agreement was noted in the MVV test values of the emphysema group subjects and those of Prime and Westlake,[6] but some discrepancies in the alveolar pCO_2 were present.

The respiratory center in pulmonary emphysema is described in standard textbooks[7] as being relatively insensitive to carbon dioxide, whereas differing opinions are to be found in the literature suggesting that the center is actually more sensitive to this gas. This sensitivity has been evaluated in terms of the minute volume response when varying concentrations of carbon dioxide are included in the inspired gas. Scott[3] attributed the relatively slight increase in minute volume seen in emphysema to a protection afforded by increased buffering action of the body fluids. The existing relationship between the carbon dioxide retention (arterial CO_2 content measurement) and the ventilatory response to inhaled carbon dioxide was shown by Prime and Westlake[6] and Tenney,[8] who ascribed the apparent decreased sensitivity of the respiratory center to increased buffering capacity of the blood and alterations in the center itself. The concept that response can be considered in terms of the patient's limiting respiration capacity has been pointed out by Holman and Shires,[9] who used a ratio "respiratory effort"

$$\left(\text{Respiratory effort} = \frac{\text{ventilation [liters/minute]}}{\text{vital capacity [liters]}}\right)$$

to show that the emphysematous patient is actually more sensitive to carbon dioxide.

None of the emphysematous patients in this study failed to demonstrate an increase

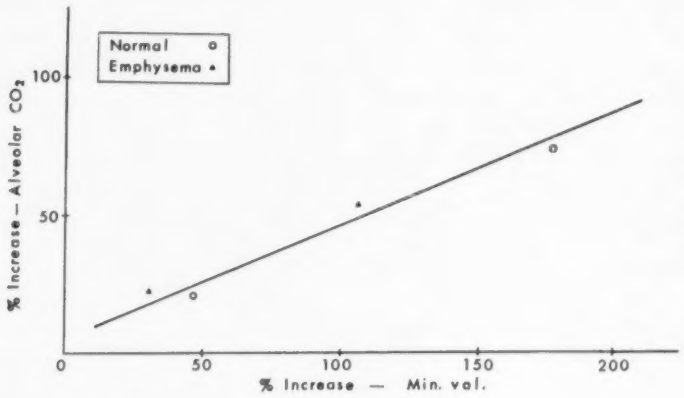

Fig. 3.—Relationship of per cent increase in minute volume to per cent increase in alveolar CO_2 while breathing 2.5% CO_2 and 7.5% CO_2 mixtures.

in minute volume when stimulated with 7.5% CO_2 in 92.5% O_2. The minute volume was doubled in these patients, and therefore severe depression of the respiratory center was not present. In a similar situation, the normal subjects trebled their resting minute volumes. This could be interpreted as a decreased sensitivity of the respiratory center in the emphysematous group, but such a conclusion does not take into consideration the immobility and inelasticity of the respiratory structures. A comparison of the maximum minute volume following 7.5% CO_2 stimulation with the MVV test value showed that the normal group utilized only one-third while the emphysematous group utilized two-thirds of their maximal ventilatory capacity. This confirms the impression of Holman and Shires,[9] since the emphysematous person is relatively more sensitive to carbon dioxide.

By relating the per cent increase in minute volume to the per cent increase of CO_2 in the alveolar gas, while breathing the 2.5% carbon dioxide and the 7.5% carbon dioxide mixtures (Fig. 3), another evaluation of their stimulating effect on respiration was made. A linear relationship existed for both normal and emphysematous mean values. Although the speed of response is not considered here, it appeared that there was no difference in the sensitivity of the respiratory centers in these groups. Other concentrations of carbon dioxide are to be evaluated to verify this relationship and to determine whether it exists at higher concentrations of the gas.

There was no significant difference between the ventilatory response of the normal group and the emphysematous group breathing 2.5% CO_2. This may be due partly to the wide variation in response to the lower percentage CO_2 shown by the normal persons, confirming the findings of Holman and Shires.[9] Using 4% CO_2 Donald and

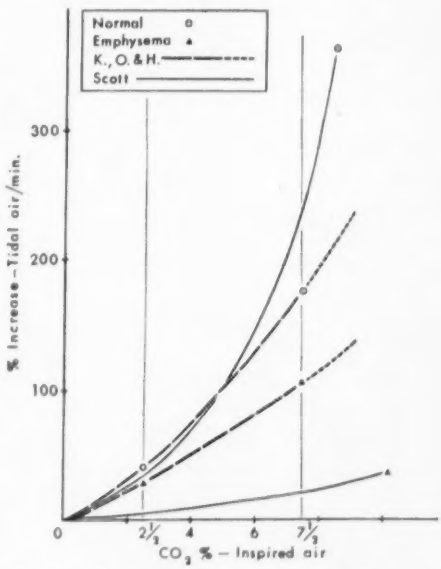

Fig. 4.—Comparison of Scott's data with data from present study, using 2.5% and 7.5% CO_2 inhalation mixtures.

Christie [4] obtained at least a 60% increase in all the normal subjects. It is not clear why some normal persons are stimulated by 2.5% CO_2 while others are only slightly affected. If the inhalation period were prolonged, perhaps the normal group would have shown a significant increase in minute volume. Because of the wide variation in response to 2.5% CO_2, this concentration has less value as a respiratory stimulant for purposes of differentiation than higher concentrations. However, the minute volume response to the 7.5% CO_2 mixture showed a marked difference between the two groups. Comparison of the present data with those of Scott revealed a close parallel to the normal curve shown by him (Fig. 4). On the other hand, the emphysema group gave a greater response than the two emphysematous persons whom he studied. Since the degree of emphysema in the present group probably was not as severe, it may be concluded that the degree of response to higher concentrations of carbon dioxide will indicate the severity of the disease.

The reason for the failure of the minute volume to decrease when the emphysema group was changed to oxygen after air is not clear. In contrast, the mean alveolar pCO_2 decreased approximately to the same extent in both the normal and the abnormal group, whereas Prime and Westlake found an increase in the arterial pCO_2 of their normal group. If a depressing effect on respiration due to a change in pCO_2 had occurred, an increase in the alveolar pCO_2 would be expected. The time interval may have influenced the results, since the patients in this series were on oxygen only 5 minutes, while those of Prime and Westlake breathed oxygen for a 30- to 40-minute period.

The alveolar pCO_2 at the end of each test period and at the end of the MVV test always showed a higher concentration in the emphysema patients. Some of the more severely emphysematous persons were observed to have alveolar pCO_2 concentrations as high as 70.5 mm. Hg while breathing the 7.5% CO_2 mixture. Analysis of the expiration curves obtained during these test periods will be presented in detail later. These maximum expiration CO_2 curves may be most useful in differentiating between normal and emphysematous persons.

The difference between the alveolar carbon dioxide measurements taken before and immediately after the MVV test reflects the ability of the subject to move carbon dioxide. Although the emphysematous patient increases his minute volume, this increase is inadequate to remove effectively the relatively greater amount of available carbon dioxide. The degree of lowering of the alveolar pCO_2 effected during this maximal effort is influenced by the severity of emphysema. During the MVV test, the normal group exhibited more than a 50% greater lowering of the pCO_2 than the emphysema group. Some of the more severely emphysematous persons were observed to have about the same alveolar pCO_2 after the 20-second maximal effort as before the test. This was attributed to the mobilization of high concentrations of CO_2 from poorly ventilated areas of the lung as well as rapid diffusion of gas across the normal alveolar membrane. The elimination of carbon dioxide from the emphysematous lung is poor in spite of the elevated pCO_2. This is demonstrated by the total quantity of carbon dioxide eliminated during the MVV test. Approximately 115 ml/minute less carbon dioxide was eliminated by the emphysema group than by the normal group.

While it is evident that many of these tests demonstrate a difference between the emphysematous patient and the normal subject, the measurement of the resting alveolar CO_2, the MVV test with CO_2 determinations before and after, and the ventilatory response to 7.5% carbon dioxide in oxygen offer an opportunity for making a more precise evaluation of the patient. These tests are of importance because they are dynamic and measure the functional profile of patients with varying degrees of emphysema. The primary emphasis of these tests

is on the measurement of carbon dioxide, the gas of basic importance in the abnormal physiology of the disease. The carbon dioxide measurements are easily accomplished.

Conclusions

1. The alveolar carbon dioxide concentration measured at rest, before and after the MVV test, has proved valuable in differentiating the emphysema group from the normal.

2. The maximum minute volume response measured with the subject breathing 7.5% CO_2 in 92.5% O_2 is a sensitive method for determining the patient's effective ventilatory response and separating emphysema from the normal state.

3. There is a highly significant correlation with the results of the alveolar carbon dioxide determinations and the timed vital capacity and the MVV test.

Summary

The results of studies of a selected group of 22 emphysematous and 20 normal patients examined in a respiratory physiology laboratory are presented.

Standard respiratory function test results are correlated with alveolar carbon dioxide measurements made at various points during the testing procedure. Patients were required to breathe air, oxygen, and various concentrations of carbon dioxide in oxygen. The alveolar carbon dioxide concentration measured at rest, before, and immediately following the maximum ventilatory volume test was statistically significant in differentiating the emphysematous group from the normal. The maximum minute volume response measured with the subject breathing 7.5% carbon dioxide in oxygen is a sensitive method for determining the patient's effective ventilatory response. The alveolar carbon dioxide determinations show highly significant correlations with the results of the standard vital capacity and maximum ventilatory volume tests.

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A Hemodynamic Concept of Atherosclerosis, with Particular Reference to Coronary Occlusion

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The primary relation of hemodynamics to the inherent pathology of atherosclerosis is the subject of the present communication. Hemodynamic factors can account for the characteristically patchy distribution of atherosclerotic lesions and the relative freedom from atherosclerosis in apparently identical adjacent areas of intima. Local factors, based upon the laws of hydrodynamics, can account for the varied pathologic appearance of arterial occlusive disease in the aorta and coronary arteries, as well as in arteries of the viscera and extremities.

The distribution of atherosclerotic lesions indicates strongly that there are certain points of predilection. Such points of predilection are determined by the nature of the motion of fluids, in this case the blood. The incidence and degree of atherosclerosis at typical areas of predilection have been recorded in 100 consecutive autopsied cases (Table). Hemodynamic atherosclerotic lesions occurred in more than one location in 90% of cases examined. The incidence, location, and degree of hemodynamic atherosclerosis appear to be related chiefly to age. Hemodynamic atherosclerotic changes were present in 100% of persons over 40 years of age. The contributing atherogenic effects of other factors, such as sex, race, habitus, diet, nutritional status, lipid metabolism, drugs, hormones, associated illnesses, and stress, require further evaluation. It is suggested that these factors may modify the primary hemodynamic mechanism.

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The motion of fluids[1] may be of two kinds, namely, streamline or turbulent. In streamline or laminar motion the particles move in definite paths. In turbulent motion the fluid moves in an eddying mass and the motion at a given point varies in an irregular manner from instant to instant. At low velocity the motion of fluid is usually streamline. As the velocity is increased the motion breaks down and becomes turbulent. Whenever lines of flow are converging, as in the arterial tree generally[2-6] or in an area of an atherosclerotic plaque, there is a tendency toward stability or streamline flow. In such tubes with converging boundaries the velocity of flow is increasing and the static pressure is decreasing.[7-9] These forces are the basis for Bernoulli's theorem, which states that fluid in motion possesses energy by virtue of its velocity and its pressure. The static pressure plus the velocity pressure is constant if fluid flows from Point 1 to Point 2 and if there is no loss of energy between these two points. Thus, as in a Venturi meter (Fig. 1), flow in a tube with converging boundaries causes the static pressure to be reduced at the narrow portion, where the velocity pressure is increased. In curvilinear motion the varying increase in static pressure is greater along the outside curvature by virtue of the centrifugal force (Fig. 2). The decrease in static pressure on the inner curvature is directly proportional to the same centrifugal force. Finally, since the velocity of flow at a cross section of a tube increases from the wall toward the center, the impingement of the more central blood stream upon a site of branching or bifurcation causes an increase in velocity pressure and decrease in

One Hundred Consecutive Autopsy Cases: Incidence and Degree of Hemodynamic Atherosclerosis at Areas of Predilection

Case	Age	Male	Female	White	Negro	Abd. Aorta	Comm. Iliac	Int. Iliac	Left Cor.	Left A.D.	Left Circ.	Rt. Cor.	Cause of Death
1	25	•		•		+	+	0	+	0	0	+	Narcotism
2	35	•			•	+	+	++	0	0	0	0	Narcotism
3	65	•			•	++++	++++	+	+	+	++	+	Trauma
4	37	•			•	+	++	+	+	+	+	0	Trauma
5	37		•	•		+	+	0	+	0	0	0	Sepsis, ab.
6	72		•	•		++++	+++	+	+++	+	+	++	Cardiac
7	25	•			•	0	0	0	0	0	0	+	Barbiturates
8	78	•		•		++++	++++	+++	++	++	0	++	Cardiac
9	42	•			•	+	0	0	+	+	0	0	Cardiac
10	57	•		•		+	0	0	+	0	0	0	Cirrhosis
11	70	•		•		+++	+++	++	+	++	0	++	Cardiac
12	35	•		•		++	+	+	0	+	0	0	Trauma
13	50		•	•		++	0	0	0	0	0	0	Carcinoma
14	45		•		•	0	0	0	+	++	0	++	Pneumonia
15	44	•			•	++	++	+	+	++	++	++	Trauma
16	68	•		•		++++	+++	++	+++	+++	+++	+++	Cardiac
17	58		•	•		+++	++	++	++	++	++	+	Trauma
18	55	•		•		+++	++	+	++	++	++	+	Drowning
19	15	•			•	0	0	0	0	0	0	0	Narcotism
20	20	•			•	0	0	0	0	0	0	0	Narcotism
21	44	•		•		++++	+++	++	+++	++++	++++	+++	Cardiac
22	55	•			•	+++	++	+	+	0	0	0	Trauma
23	37	•			•	0	+	0	0	0	0	0	Brain hemorr.
24	40		•	•		++	+	0	+	+	0	0	Trauma
25	59	•		•		+++	++	+	++	++	+++	+	Trauma
26	62	•		•		++++	+++	+++	+++	+++	++++	+++	Trauma
27	45	•		•		++	++	++	++	++++	+++	+++	Cardiac
28	24		•	•		+	+	+	+	++	+	0	Barbiturates
29	48	•			•	+++	++	++	++	+++	+++	++	Brain hemorr.
30	50	•		Yellow		++	+	0	0	0	0	0	CO poisoning
31	42	•		•		+++	+++	+	+	++	++	+	Trauma
32	59	•		•		++	++	+	+	++	++	++	Pneumonia
33	56		•	•		++	+	++	++	+++	++	+	Barbiturates
34	73		•	•		++	++	+++	++	+++	++	+	Cardiac
35	60	•		•		++	+	+	++	+++	+++	++	Meningitis
36	39	•		•		++++	+++	++++	++++	++++	++++	++++	Cardiac
37	45	•		•		+++	++	+	++	++	+	++	Trauma
38	60	•		•		++++	++	+++	++	+++	+	+++	Uremia
39	52	•		•		++++	++++	+++	+	++	+	++	Cardiac
40	41	•			•	+	+	0	++	++	0	0	Alcoholism
41	76		•	•		++++	+++	++++	++	+++	+	+++	Intest. obst.
42	21	•		•		+	0	0	+	+	0	0	Trauma
43	34	•			•	+	0	0	+	+	0	0	Tetanus
44	70	•		•		+++	++	+	++	++	++	+	Trauma
45	24		•	•		+	+	0	0	+	+	0	Postpartum hem.
46	48	•		•		+++	++	+	+	+	0	0	Trauma
47	33	•			•	++	+	0	++	++	+	++	Trauma
48	67		•	•		++	++	0	++	++	++	+	Splenectomy
49	33	•			•	++	+++	++	++	++	++	++	Cardiac
50	85	•		•		++++	++++	++	++	++	+	+	Trauma
51	85		•	•		++++	++++	++++	+++	++++	+++	+++	Cardiac
52	30	•		•		+	0	0	+	+	0	0	Trauma

One Hundred Consecutive Autopsy Cases: Incidence and Degree of Hemodynamic Atherosclerosis at Areas of Predilection—Continued

Case	Age	Male	Female	White	Negro	Abd. Aorta	Comm. Iliac	Int. Iliac	Left Cor.	Left A.D.	Left Circ.	Rt. Cor.	Cause of Death
53	70	•		•		++++	+++	++++	++	+++	+++	+++	Barbiturates
54	33	•			•	+	+	0	+	+	0	0	Trauma
55	48	•		•		+++	+++	0	+	+++	+++	++	Trauma
56	69	•		•		++++	++++	++++	+	+	0	0	Trauma
57	25	•			•	0	0	0	+	0	0	0	Narcotism
58	62		•	•		++	+++	++	++	+++	0	++	Trauma
59	61	•		•		+	+	+	0	+	0	+	Cirrhosis
60	41		•		•	+++	+	+	++	++++	+	+	Cardiac
61	27		•	•		+	+	0	+	+	0	0	CO poisoning
62	60	•		•		++++	++++	+++	++	++++	+	+++	Trauma
63	53	•			•	++	++	++	+	++	++	++	Trauma
64	67	•		•		++++	++++	++++	+++	++	+	+	Trauma
65	35	•			•	++	+	0	+	++	++	+	Trauma
66	54	•		•		+++	+++	++++	++	+++	++	++	Brain hemorr.
67	48		•		•	+	+	0	0	+	0	0	Trauma
68	60		•	•		++++	+++	++++	++	++++	++	++++	CO poisoning
69	61	•		•		+	+	0	++	+	+	++	Trauma
70	77	•		•		++	+	+	+	++	+	+	Trauma
71	68		•	•		++++	++++	+++	++	++	+++	++	Cardiac
72	50	•		•		+	+	0	+	+	0	0	Alcoholism
73	46		•		•	+	+	0	+	++	0	0	Trauma
74	31		•		•	+	0	0	0	0	0	0	Trauma
75	51	•		•		++	+	0	+	++	0	++	Trauma
76	60	•		•		+++	+++	+++	++	+++	++	++	Cardiac
77	25		•	•		+	0	0	0	0	0	0	Trauma
78	52	•		•		++	+	0	+	++	0	0	Alcoholism
79	65	•		•		++++	++++	++++	++	+++	++	++	Trauma
80	25	•			•	0	0	0	++	0	0	0	Drowning
81	69		•	•		++++	++++	++++	++	++++	++++	++	Cardiac
82	60	•		•		+	+	0	+	++	++	++	Trauma
83	19		•	•		0	0	0	0	+	+	0	Trauma
84	59	•		•		++++	++++	+++	+	++	++	++	Trauma
85	55	•		•		++++	++++	+++	0	++++	++	++++	Trauma
86	49	•		•		++	++	0	++	++	++	++	Cardiac
87	35	•			•	++	++	+	++	++	0	++	Alcoholism
88	70	•		•		+++	++	++++	+++	++++	+++	++++	Carcinoma
89	12	•		•		0	0	0	0	0	0	0	Trauma
90	70	•		•		++++	++++	+++	+	+++	+	++++	Trauma
91	58		•	•		++++	++++	+++	++	++++	++++	++++	Trauma
92	69	•		•		++	++	++	+	++	++	++	Mesenteric throm.
93	29	•		•		+	+	+	+	++	+	+	Alcoholism
94	44	•			•	++	+	+	++	++	++	++	Brain hemorr.
95	32	•		•		+	+	0	++	+++	++	++	Alcoholism
96	58		•		•	+++	++++	+++	++	++++	++++	+++	Trauma
97	34	•			•	+	+	0	0	0	0	0	Trauma
98	40	•			•	+	+	0	++	0	0	0	Brain hemorr.
99	69	•		•		++++	+++	++++	++	+++	+++	++	Carcinoma
100	89	•		•		++	+++	+++	++	+++	++	++++	Cardiac

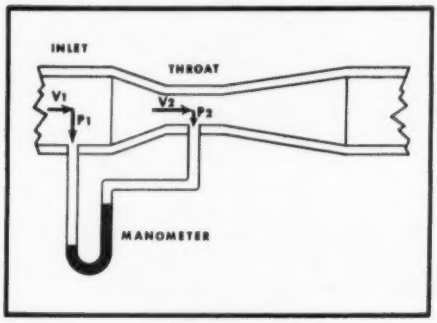

Fig. 1.—Venturi meter.

Fig. 2.—Elbow flow meter.

static pressure at the medial walls of the crotch zone.

Physical factors formulated in Bernoulli's theorem are the basis for such diversified practical aplications as flight in the air due to the lift of an airfoil (Fig. 3) and innumerable hydraulic devices utilizing differences in pressure or suction effects. Similarly, the physical factors based upon Bernoulli's theorem clarify the predilection for atherosclerotic lesions to occur at areas in the circulation characterized by converging boundaries (Fig. 4), branching (Fig. 5), bifurcation (Fig. 6), abrupt curves (Fig. 7), and points of external attachment (Fig. 8). At these points the arterial blood flow is subject to an increase in velocity pressure and a decrease in static pressure.

The local decrease in static pressure may be considered a suction effect which produces the initial tendency for the vessel to be narrowed by motion of the wall toward the center of the lumen (Fig. 3). This gives rise to the initial reaction of intimal thickening. At such areas of intimal thickening continued exposure to the increase in velocity pressure and decrease in static pressure, or suction effect, stimulates further changes. These lead to the formation of a well-defined atherosclerotic plaque which eventually assumes its characteristic appearance. This process involves the lining endothelial layer, the subendothelial fibrous layer, variable accumulations of lipids, cellular infiltration, and frequent calcification. Capillary vascularization from the lumen and the vasa vasorum may occur. The atherosclerotic plaque is subject to motion due to the varying suction effect which is dependent upon the velocity of blood flow at the area of narrowing and not necessarily directly related to the systemic blood pressure. When the pathologic degenerative changes in the atherosclerotic plaque have reached a critical point, the local increase in velocity of flow with corresponding decrease in static pressure may cause detachment of the intimal layer. This may produce a raw or ulcerated atheromatous surface which, in contact

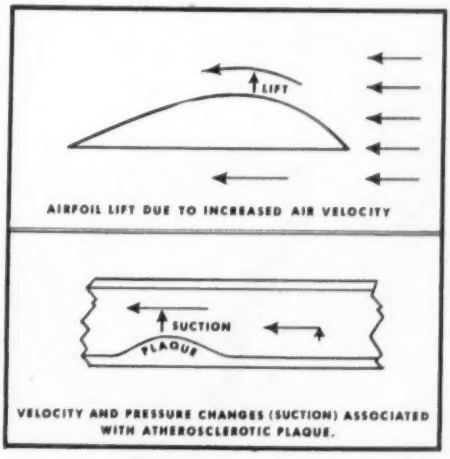

Fig. 3.—Similarity of dynamic factors involving an airfoil and an atherosclerotic plaque.

Fig. 4.—Left coronary artery, anterior descending branches. The "converging boundary" lesion produces concentric atherosclerosis; "branch" and/or "curvature" lesion produces eccentric atherosclerosis.

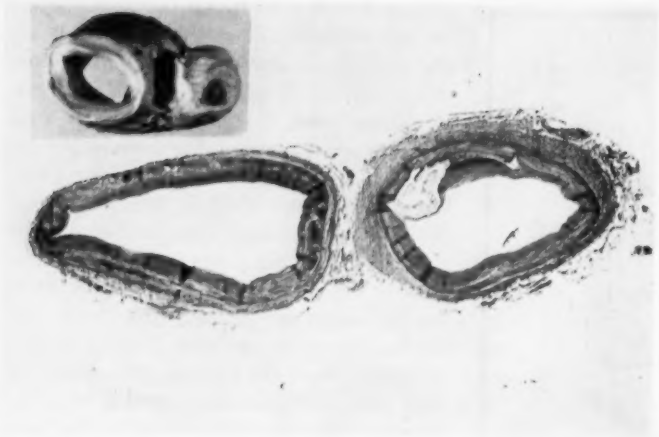

Fig. 5.—Atherosclerosis of the medial wall of the internal iliac (hypogastric) artery—a "branch" lesion.

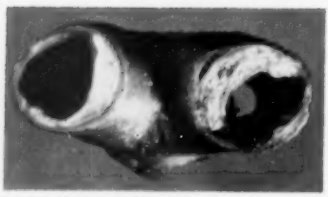

Fig. 6.—Atherosclerosis of the medial walls of the common iliac arteries—a "bifurcation," "Y," or "crotch" lesion.

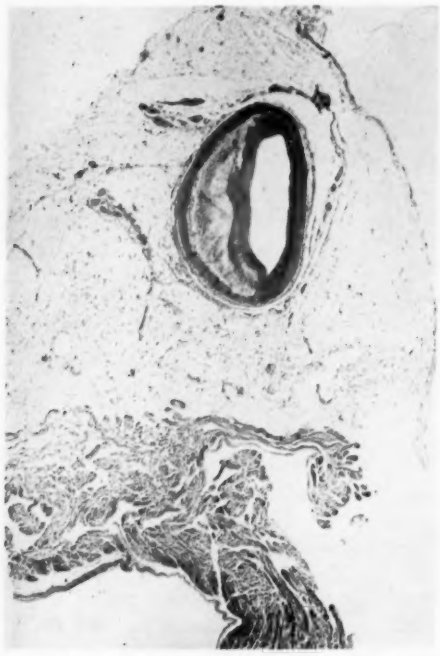

Fig. 7.—Atherosclerosis of the internal wall of the right coronary artery in the A-V sulcus near the acute border of the heart—a "curvature" lesion.

with the flowing blood, results in the formation of a mural thrombus at this site.

This hemodynamic mechanism may account for the location of an atherosclerotic plaque and its progressive pathologic evolution. The composite effects of velocity of blood flow, external attachment, caliber of the lumen, degree of curvature, and branching characteristics determine the sites of predilection.

Varying types and degrees of occlusion may follow and may be further influenced by additional factors: 1. Coronary occlusion may result solely from progressive intimal thickening or atheromatosis. Pathologic examination of such occluded coronary arteries will disclose that the atheromatous process developed at a site of predilection influenced by increased blood velocity, impingement of blood flow, or curvature. A relatively free and straight vessel may show correspondingly more concentric atherosclerosis. The nature of flow in a zone of sharp curvature determines the greater degree of involvement of the internal radius in comparison with the external radius (Fig. 7).

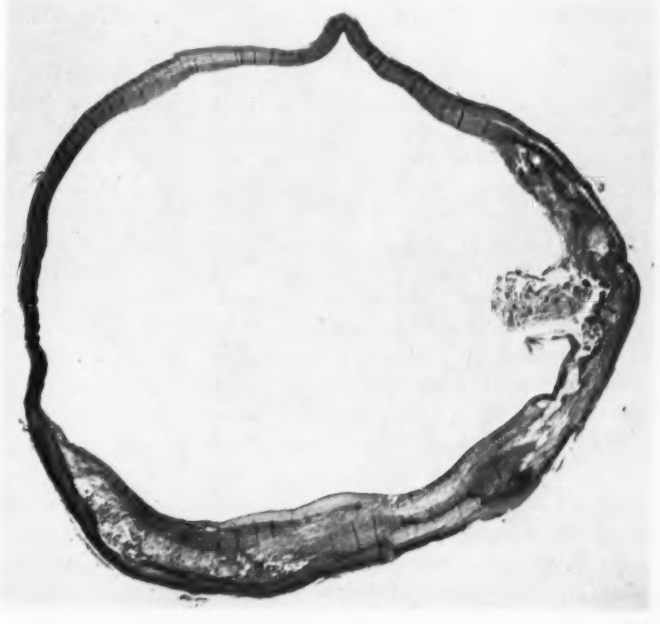

Fig. 8.—Atherosclerosis of the dorsal wall of the abdominal aorta—an "attachment" lesion.

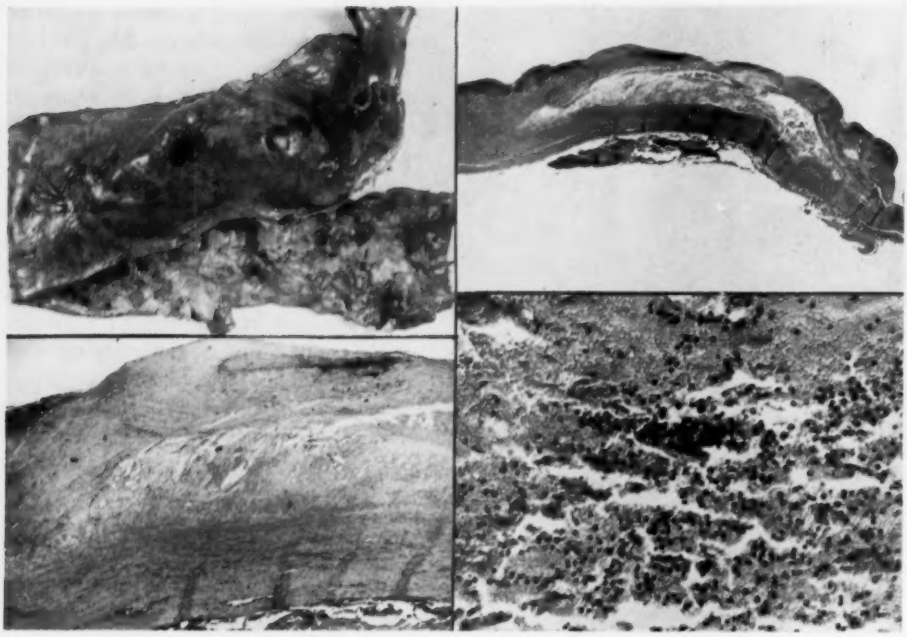

Fig. 9.—Aortic arch showing adventitial hemorrhage.

The free epicardial arc of an involved coronary artery may be less affected than the attached myocardial arc. The reduced lumen at the site of such atherosclerotic change will be, of necessity, eccentrically placed. 2. The local increase in blood velocity and decrease in static pressure at the site of an atherosclerotic plaque cause movement of the vessel wall with a tendency for the plaque to be drawn toward the center of the lumen. This mechanism may account for hemorrhage in the adventitia (Fig. 9), media, or intima of atherosclerotic vessels. Intramural hemorrhages occur most frequently within atherosclerotic plaques. The occurrence of a subintimal hemorrhage in an atheromatous plaque is a complication which may further contribute to the occlusive changes.[10] 3. The increased blood velocity and decreased static pressure at the site of a soft atherosclerotic plaque may shear off and embolize the superficial intimal layer or the contents of a plaque. This exposes a raw, irregular atherosclerotic ulcer surface to which blood elements become attached to form a thrombus, which may be occlusive.

The flow of blood in the coronary arteries is intermittent [11] as a result of systolic contraction. The stream is subject to rapid changes in velocity, increased flow occurring during diastole, and markedly reduced flow during systole. The coronary arteries appear to be unique in the body with respect to such phasic variations in blood flow. It is also notable that the caliber of the extramural coronary arteries tapers rapidly. These may be significant factors in their predisposition toward atherosclerotic changes.

It appears from the above-described hemodynamic mechanisms that occlusive changes in the coronary arteries are the sequelae of fluid dynamics applied to the natural conditions of the coronary circulation.

It is noteworthy that the elasticity of the arch of the aorta serves to produce streamline flow by stabilizing the pressure and velocity of flow through its action as a surge

Fig. 10.—Dissecting hemorrhage (hematoma) of the aorta (by permission of Dr. H. B. Burchell, Mayo Clinic, Rochester, Minn.).

chamber. The predilection of the aortic arch for atherosclerotic change and dissecting hematomas [12] appears determined by the markedly increased velocity pressure and reduced static pressure or suction effect in this region. The sudden release of intra-abdominal pressure in the Valsalva maneuver causes the aortic blood velocity to increase greatly. The accompanying suction effect may tear the aortic wall and produce a dissecting hematoma (Fig. 10). The reverse of these conditions is present in the large veins of the body including the pulmonary artery. The pulmonary ring and adjacent pulmonary artery have a greater circumference than the aortic ring and ascending aorta. Since, normally, the same volume of blood per unit of time must pass these orifices, it is obvious that the velocity of flow is diminished in the pulmonary artery. This is associated with a relative increase in lateral pressure. Therefore, atherosclerosis due to the suction effect of the stream in the pulmonary artery is minimized. In veins, which generally present diverging lines of flow, the velocity pressure is relatively low and the static pressure is relatively high. The suction action upon the walls of veins is therefore minimal, and occlusive sclerotic changes are comparatively rare.

Relation to Stress, Emotion, and Effort

The velocity and volume of blood flow in the coronary arteries are increased when the body requires the heart to increase its rate. With increasing tachycardia the volume and velocity of coronary flow eventually diminish because of the shortened diastole. Similarly, a strict correlation between heart rate and cardiac output does not take place, the output rising with increasing heart rate until a critical point is reached at which the cardiac output is reduced by the small stroke volume. If the velocity of coronary blood flow is increased by episodes of exertion, emotion, or stress, then the possibility exists that a previously existing atherosclerotic plaque could undergo anatomic change as a result of the decrease in static pressure at this point. This effect would be immediate with respect to intramural hemorrhage or ulceration of an atherosclerotic plaque with thrombus formation. From the standpoint of clinical correlation this could be the mechanism of some sudden deaths due to acute coronary occlusive disease with antecedent progressive coronary atherosclerosis. This may be the mechanism for acute coronary occlusion with myocardial infarction which appears to follow upon very strenuous exertion or extreme emotional disturbance. It should be emphasized that sudden death can occur from coronary insufficiency incident to exertion or emotion without sufficient time for myocardial infarction to result. Coronary insufficiency may precipitate a fatal arrhythmia, such as cardiac standstill or ventricular fibrillation. Also, coronary insufficiency may progress to myocardial infarction without any additional acute occlusive process. An exertional or emotional episode which produces hemodynamic alterations sufficient to cause acute complications of the preexisting sclerotic disease of the arteries should result in bridging symptoms between the episode and the subsequent development of

myocardial infarction or death. If an interval elapses without significant symptomatology the causal relation would be speculative. In the absence of bridging symptoms there does not seem to be sufficient reason to relate myocardial infarction or death due to occlusive coronary artery disease, with or without acute luminal thrombosis or intramural hemorrhage, to a previous episode of stress which may have produced a transient increase in velocity or decrease in static pressure of coronary blood flow. The natural course of occlusive coronary artery disease influenced by the wide range of hemodynamic changes in the coronary circulation can account for all but the most exceptional cases of myocardial infarction or death due to coronary occlusive disease.

Summary

Hemodynamics has been presented as a primary factor in the development of atherosclerosis. A physical basis for occlusive coronary artery disease is offered. A mechanism is described for intimal ulceration, intramural hemorrhage, and dissecting hemorrhage occurring as complications during the pathogenesis of atherosclerosis. Atherosclerosis would appear to be a sequel primarily of fluid dynamics applied to the natural conditions in the circulatory system. A clinical and pathological correlation of cardiac stress is discussed.

The American Heart Association and its Committee on the Effect of Strain and Trauma on the Heart and Great Vessels made facilities for this study available.

3 E. 68th St. (21).

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A New Method for Determining the Portal Circulation Time

The Spleen-Lung Ether Time

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The methods used up to the present to calculate the speed of the portal circulation have been the following: Serial splenoportography, the injection into the spleen of radioactive sodium and subsequently detecting its absorption by the liver, and, finally, the method of Newman and Cohen,[3] which consists of the injection of ether vapors into the rectum, after which the time it took to detect the smell of ether from the patient's breath is measured.

The first method, the splenoportography, not only enables one to calculate the circulation time but also gives us an x-ray picture of the portal tree. The second method mentioned is a more exact one but requires a more elaborate technique, which is not easily carried out in the ordinary practice. Lastly, the procedure of Cohen and Newman has obvious inconveniences; also, one cannot be sure if the ether is readily absorbed by the intestine. Even if it is, the existence of certain communications between portal and caval systems do not permit us to conclude definitely if the ether passes exclusively through the portal bed.

Since about eight months ago we have been utilizing a new and simple technique which in our opinion is quite useful. It consists of the injection of a small quantity of ether into the spleen by a transparietal route, determining subsequently the spleen-lung circulation time. Before or after this first step the circulation time between the arm and lung is also determined by ether inoculation. We have found no previous reference in the literature which we have been able to review about the utilization of this technique. Our first results with this technique have been reported in the second Luso-Spanish Congress of Cardiology, held in Lisbon.

In normal persons and in different diseases we have made determinations of the arm-lung circulation time, the spleen-lung circulation time, and the intrasplenic pressure, and we also have performed a serial transparietal splenoportography.

Procedure

Following the technique proposed by Abeatici and Campi, we performed the transparietal puncture of the spleen, after which, having assured ourselves that the needle was precisely in this organ, we proceeded to determine at once the intrasplenic pressure, utilizing a modification of the Claude manometer. Immediately after, we injected in less than one second a mixture of 1 cc. of ether with 2 cc. of isotonic saline solution, after which we determined the time between the injection and the first perception of the ether in the expired breath (spleen-lung circulation time). Subsequently, in the same session, a few minutes after, we made serial splenoportographies by injecting about 30 to 40 cc. of contrast and taking x-ray films every 1 or 2 seconds, up to 10 seconds in normal cases and up to 30 seconds in patients in whom we suspected the presence of some processes capable of altering the portal circulation time.

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With this method we were able to make a comparative study of the morphology and the dynamics of the portal circulation. One of the most important findings that we have observed by the studies carried out with this new technique for determining the spleen-lung circulation time with ether, in relation to the data obtained from the serial splenoportography, is the existence of some discrepancy, probably caused by the possibility which exists at times that the iodine contrast injected into the spleen continues to penetrate into the portal territory after having completed the injection of the contrast. The presence of this phenomenon can be explained either by the contraction of the spleen or by what is more probable, the contraction of the splenic capsule, as contrast medium can be found localized predominantly under the capsule of the spleen in cases in which there has been a lack of parallelism between the arm-lung ether time and the emptying time of the portal territory, as observed by splenoportography.

Initially we carried out our studies in 10 controlled normal subjects, the results of which we include in Table 1. Only in 6 of the 10 normal cases did we do serial splenoportographies, as we had been able to confirm the observations of Abeatici and Campi[1] that the contrast disappears from the portal territory in less than four seconds. Curiously, in one of our cases who had a spleen-lung circulation time of four seconds we were able to observe a permanence of the contrast in the portal territory up to eight seconds, as can be seen in the data of Table 1. It should be noted that the contrast appeared near the limits of the splenic capsule,

TABLE 1.—*Findings in Normal Subjects*

Arm-Lung Time, Sec.	Spleen-Lung Time, Sec.	Splenic Pressure	Persistence of Contrast in Splenoportography, Sec.
7	6.5	12	2
6	5.5	11	3
5	5	11	2
6.5	6	12	8
6	6	13	2
6.5	6	12	4
5.5	5	10	
5	4.5	10	
4.5	4	10	
7	6.5	12	

TABLE 2.—*Findings in Patients* Periportal Cirrhosis

Arm-Lung Time, Sec.	Spleen-Lung Time, Sec.	Splenic Pressure	Persistence of Contrast in Splenoportography, Sec.
Periportal Cirrhosis			
8	19	39	19
7	17	40	16
8	19	42	26: distention of capsule by contrast.
6	14	32	13
7	18	38	16
Biliary Cirrhosis			
5	9	20	11
7	12	43	10
Banti's Syndrome			
7.5	12	52	No contrast passes to the porta
Posthepatitis Cirrhosis			
8	11	15	Disappeared after 10
Hemochromatosis			
6	14	40	14
Metastatic Neoplasm of Liver		**Old Calcified Hydatid Cyst**	
7	7	36	7

thus favoring our hypothesis that when such a disparity exists between the spleen-lung circulation time and a more prolonged persistence of contrast, it is due to an autopropulsion or autoinjection of the contrast as a result of the intracapsular tension after the injection of the contrast has been completed. The other possibility is that the ether flows through a short circuit. This, however, is not compatible with the absence of collateral circulation in these normal subjects and with the fact that many other authors have established that the contrast usually disappears in from three to four seconds. The only exceptions are the results obtained by the school of Pedro Pons and collaborators, who report in certain cases the permanence of contrast for as long as eight seconds. This fact undoubtedly is difficult to explain except through our hypothesis. Furthermore, the findings referred by Hunt[2] (by means of the injection of radioactive sodium) show that the speed of circulation in the portal territory in normal subjects is about 10 cm. per second. We have determined the circulation time and intrasplenic pressure and have done serial splenoportographies in 10 cases of cirrhosis (Table 2).

From the study of these cases we can see that there is a slowing of the portal circulation in cirrhotic patients which is especially evident in the Laennec type, where we find it more marked than in biliary cirrhosis. In a patient with cirrhosis and Banti's syndrome, probably produced by a thrombophlebitis of the splenic vein which had been operated on, it was not possible to fill the portal territory; the spleen-lung time was 12 seconds. In a patient with a metastatic neoplasm of the liver the determinations were practically normal.

Comment

Our experience is yet quite limited, in order to derive from it definite conclusions, but we believe, however, that it is sufficient to point out the value of this simple procedure for determining the circulation time between the spleen and lung by means of the direct injection of ether.

From the results obtained with normal persons and in 11 patients, 10 of them with cirrhotic lesions, we found that there is usually a direct relationship between the time it takes for the contrast medium to disappear from the portal territory, as can be seen by serial splenoportographies, and the data obtained by the simpler and more reliable procedures, which consist of determining the spleen-lung ether time. Only in one normal subject and in one patient with cirrhosis was there a clear discrepancy between findings, in the sense that the spleen-lung time was much shorter than what is usually observed by means of splenoportography. Precisely in both, the contrast medium accumulated, quite evidently, not only within the splenic parenchyma, but also below the capsule, causing a distention of it.

Summary

We believe that the determination of the spleen-lung ether time is a more reliable, easier, and more precise procedure than splenoportography for the study of the dynamics of the portal circulation. In normal subjects the spleen-lung ether time is approximately one or two seconds less than the arm-lung ether time.

In five patients with cirrhosis of the Laennec type, we found a marked increase of the spleen-lung circulation time as compared with the arm-lung time, which in certain cases was even more than double. In two patients with biliary cirrhosis, the slowing of the portal circulation was not as marked as in the cases of cirrhosis of the Laennec type, but it was, however, markedly increased in a case of posthepatitis cirrhosis, where the difference was very small (three seconds). In a case of hemochromatosis the spleen-lung time was somewhat more than double. In a patient with a metastatic neoplasm of the liver the ether time was normal.

We should point out that in one of our patients with a clinical history of obscure abdominal pains which suggested a recurrent pancreatitis because of the finding of a prolonged spleen-lung time (ether), we were induced to study the case further, and hepatic biopsy finally proved that it was a case of cirrhosis.

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The Features and Significance of Hypertrophic Osteoarthropathy

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Introduction

Hypertrophic osteoarthropathy is usually accompanied by clubbed fingers and commonly by arthralgia, bone pain, enlargement of the hands and feet, thickening of the wrists and ankles, and gynecomastia. Although it is relatively common, some physicians are not familiar with the syndrome. Cases are sometimes misdiagnosed as acromegaly, Paget's disease, or rheumatoid arthritis. Marie's[1] first case, described in 1890, was originally diagnosed as acromegaly.

The diagnosis of hypertrophic osteoathropathy is often made by the roentgenologist. The x-ray appearance of onionskin layers or a thin line of new bone along the distal portions of the long bones is characteristic. The disease takes its name from the enlargement of the bones seen in later stages.

In past years, hypertrophic osteoarthropathy was often an incidental finding in cases of pulmonary suppuration. In a review of the world literature up to 1915, Locke[2] collected 144 cases of hypertrophic osteoarthropathy—108 of which were secondary to respiratory tract diseases, including bronchiectasis and tuberculosis. He did not list pulmonary neoplasm as a separate category, although his first case report described the symptoms of hypertrophic osteoarthropathy in a young man with carcinoma of the lung. The remainder of his cases were associated with heart diseases, liver and gastrointestinal diseases, metastatic carcinoma, and syphilis. He listed five cases that had no known associated disease.

Twenty-five papers in the English literature since 1938, reporting patients with hypertrophic osteoarthropathy, were reviewed. Of the cases reported, 79 were associated with pulmonary neoplasm and only 12 with other diseases, including empyema,[3] tuberculosis of the bone,[4] sprue and leukemia,[5] myxedema,[6] and lung abscess[7] and as an independent phenomenon.[8]

With the advent of the antibiotics, the clinical pattern of chest disease has changed. The symptoms of hypertrophic osteoarthropathy are now most often associated with carcinoma of the lung. Three recent reports have emphasized this relationship.[7,9,10]

Clubbing of the fingers in heart disease with cyanosis is a common phenomenon, but is very rarely accompanied by the clinical signs or x-ray findings of hypertrophic osteoarthropathy.[11] This clubbing is related to increased venous pooling of blood in the fingertips,[12] while in the clubbing of pulmonary disease the increased size is due to fibrous tissue.[13] This difference was demonstrated rather simply by squeezing blood from the fingers and comparing the residual size.[12]

It is the purpose of this report to describe 22 cases of hypertrophic osteoarthropathy in adults seen by us or our colleagues and to discuss the implications of the syndrome.

Analysis of Patients

Twenty-two patients with the x-ray changes of hypertrophic osteoarthropathy

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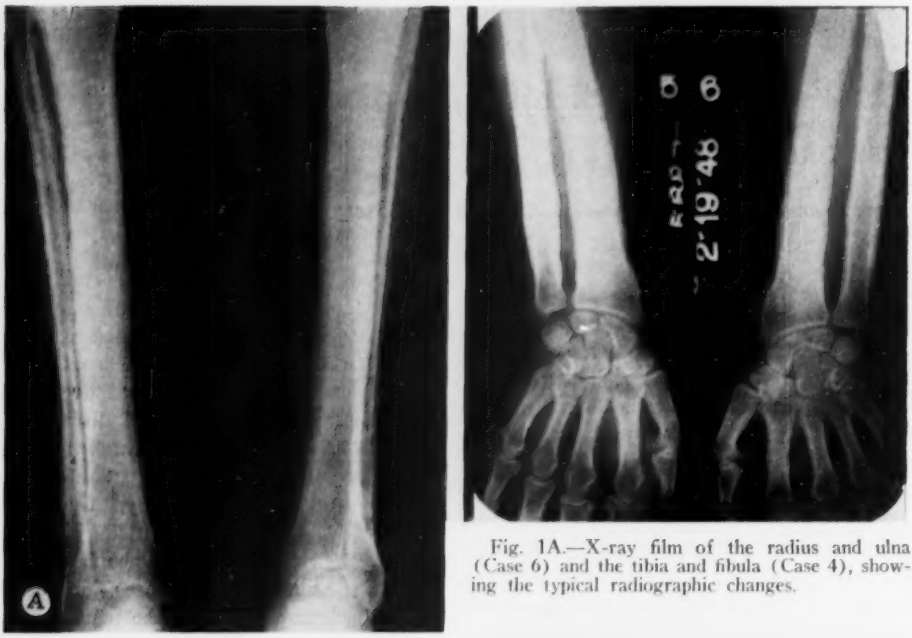

Fig. 1A.—X-ray film of the radius and ulna (Case 6) and the tibia and fibula (Case 4), showing the typical radiographic changes.

were observed during a 10-year period. Only patients with radiographically demonstrable osteoarthropathy were included in this study, and all are included in this report. (Fig. 1)

Table 1 lists some of the pertinent data regarding these patients. All patients with the exception of Cases 17 and 21 had malignancies involving the lung. Six patients had adenocarcinoma, primary in the lung, and an equal number had squamous-cell carcinoma of the lung. Three had fibrosarcoma of the lung. One patient was seen with each of the following diagnoses: Alveolar carcinoma of lung, small-cell carcinoma of lung, undifferentiated carcinoma of lung, presumptive carcinoma of lung with clumps of malignant cells seen in sputum (operation or autopsy not performed), Hodgkin's disease involving the lung and adrenals, diffuse pulmonary fibrosis, and infected pulmonary infarction.

The age distribution ranged from 24 to 83, with a mean of 59, and a preponderance in the sixth and seventh decades. The sex distribution was 21 men and 1 woman. Al-

Fig. 1B.—X-ray film demonstrating the typical appearance of new bone formation characteristic of hypertrophic osteoarthropathy.

TABLE 1.—*Data on Patients with X-Ray Changes of Hypertrophic Osteoarthropathy**

Case	Age	Sex	Final Proved Diagnosis	First Symptom	Gynecomastia	Face
1	57	M	Squamous-cell carcinoma, lung	Chest pain	0	----
2	60	M	Fibrosarcoma, lung	Joint pain	0	----
3	72	M	Fibrosarcoma, lung	Swelling, hands	+	Acromegaloid
4	58	M	Adenocarcinoma, lung	Pain and swelling, hands	0	Acromegaloid
5	24	M	Hodgkin's disease, lung and adrenals	Weakness, fever	0	----
6	53	M	Adenocarcinoma, lung	Swelling and stiffness, wrists	+	Acromegaloid
7	63	M	Alveolar carcinoma, lung	Swelling ankles	0	----
8	47	M	Squamous-cell carcinoma, lung	Cough	0	----
9	56	M	Small-cell carcinoma, lung	Joint pains	0	----
10	83	M	Carcinoma, lung, presumptive	Joint pains	+	----
11	53	M	Adenocarcinoma, lung	Joint pains	+	Acromegaloid
12	57	M	Squamous-cell carcinoma, lung	Swelling, feet and ankles	+	Acromegaloid
13	35	M	Undifferentiated carcinoma, lung	Cough	0	----
14	65	M	Fibrosarcoma, lung	Joint pains	+	Acromegaloid
15	60	M	Adenocarcinoma, lung	Joint pains and ankle swelling	+	Acromegaloid
16	66	M	Adenocarcinoma, lung	Joint pains	+	----
17	63	M	Infected infarction, lung	Cough, dyspnea, fever	0	----
18	63	M	Adenocarcinoma, lung	Joint pains	0	----
19	62	M	Squamous-cell carcinoma, lung	Pain, feet	0	Acromegaloid
20	56	M	Squamous-cell carcinoma, lung	Joint pains	+	----
21	58	F	Pulmonary fibrosis	Cough	---	----
22	73	M	Squamous-cell carcinoma, lung	Joint pains	+	----

*Case 10—Seen through the courtesy of Dr. William K. Ishmael, Oklahoma City. Cases 18 and 19—Oklahoma City Veterans Hospital. Case 19—Additional records made available through the courtesy of Dr. R. G. Jacobs, Enid, Okla. Cases 11, 12, 20, 21 and 22—University of Oklahoma Hospitals. All other cases—Minneapolis Veterans Hospital.

though 15 of the patients were seen in Veterans Hospitals, six of the remaining seven cases seen in other hospitals were men, suggesting that there may be a predilection for men.

It is significant that after the first complete examination, the correct diagnosis was made in only 3 of the 22 patients. The most frequent diagnosis applied to the joint disease was rheumatoid arthritis. Paget's disease and acromegaly were considered in several patients. The pulmonary disease was most often overlooked or considered to be a benign disease, such as tuberculosis, cyst, or unresolved pneumonia. Unfortunately, many of the patients were seen by numerous physicians before the true nature of the disease was determined.

In addition to the joint symptoms and the chest symptoms, certain other features might be considered a part of the syndrome. Gynecomastia was observed in 10 of the 21 males. Eight of the patients had alterations in facies, with prominent nose and furrowed brow, which we have termed acromegaloid (Figs. 2 and 3). Several of these persons showed a striking resemblance to each other.

The first symptoms were related to the joints in 17 instances and to the chest in 5 patients (Table 2). The most frequent joint symptom was pain, which occurred in

Fig. 2 (Case 6).—Clubbed fingers, thick forearms and legs, furrowed face, and mastectomy scars are evident.

Fig. 3 (Case 4).—The striking resemblance to the patient pictured in Figure 2 may be seen.

19 of the patients. It is noteworthy that neither of the patients with benign lung disease had joint pain, in contrast to the patients with malignancy, where pain was a symptom in 19 of 20. Clubbing occurred in all but one patient but was usually not noticed by the patient until his attention was directed to the sign. A brawny edema of the legs and periarticular swelling was found in 19 instances. Most of the patients, i. e., 17, showed a diffuse thickness of the legs or forearms or both. This thickening of the extremities was evident on inspection and palpation and was distinct from the soft-tissue edema. It appeared to be related to the bony alterations. Joint effusions occurred in six patients at some time during their course. The joints involved by the above symptoms were usually the larger joints, most frequently the ankles, knees, and wrists. The interphalangeal joints usually were spared or minimally involved. In eight patients, joint symptoms were present without any chest symptoms. The duration of joint symptoms prior to admission in this group varied from 6 to 36 months. An additional nine persons had joint symptoms preceding the chest symptoms by intervals of 1 to 57 months and usually by

TABLE 2.—*Symptoms and Findings in Extremities*

Case	Clubbed Fingers	Joint Pain	Joint Effusions	Periarticular Swelling and Edema	Thickening of Forearms and Legs	Predominant Joints Involved	Duration Joint Symptoms, Mo.	
							Before Admission	Before Chest Symptoms
1	+	+	+	+	+	Ankle, knee, wrist	2	*
2	+	+	0	+	+	Wrist	36	†
3	+	0	0	+	+	Ankle, knee, wrist	14	†
4	+	+	0	+	+	Ankle, knee, wrist	10	†
5	+	+	0	0	0	Ankle, wrist	0	1
6	+	+	+	+	+	Ankle, knee, wrist	30	†
7	+	+	0	+	+	Ankle, knee, wrist	60	48
8	+	+	+	+	+	Ankle	0	*
9	+	+	0	+	+	Ankle, wrist	10	†
10	0	+	0	+	0	Ankle, knee, wrist	36	18
11	+	+	0	+	+	Ankle, knee, wrist	18	†
12	+	+	0	+	+	Ankle, wrist	6	†
13	+	+	+	+	+	Knee	12	*
14	+	+	+	+	+	Knee	60	54
15	+	+	+	+	+	Ankle, knee	60	57
16	+	+	0	0	0	Ankle, knee, wrist	24	21
17	+	0	0	0	0	None	‡	‡
18	+	+	0	+	+	Ankle, knee, wrist	36	35
19	+	+	0	+	+	Ankle, knee, wrist	26	23
20	+	+	0	+	0	Ankle, knee, wrist	7	†
21	+	0	0	+	+	Ankle, knee	‡	‡
22	+	+	0	+	+	Ankle, knee, wrist	4	1

*Chest symptoms preceded joint symptoms.
†No chest symptoms.
‡No joint symptoms.

TABLE 3.—*Pulmonary Findings* *

Case	Chest Symptoms	Chest X-Ray: Chest Examination	Chest X-Ray: Abnormal	Chest X-Ray: Suggestive of Malignancy	Bronchoscopy	Sputum for Malignant Cells	Surgery	Carcinoma Proved First at Surgery	Autopsy Confirmation of Diagnosis
1	Hemoptysis, pain	0	+	+	0	....	Resected	+	+
2	0	+	+	+	0	....	Not resectable	+	....
3	0	+	+	+	0	....	Punch biopsy only	+	....
4	0	+	+	+	0	+	Resected		....
5	Cough	0	+	0	....	....	....		+
6	0	0	+	+	0	0	Not resectable	+	+
7	Cough	0	+	0	0	+	Resected		....
8	Cough, pain	+	+	+	+	+	....		+
9	0	0	+	+	0	0	....		+
10	Cough	0	+	+	....	+	....		....
11	0	0	+	+	....	0	Resected	+	....
12	0	0	+	+	....	+	Resected		....
13	Cough	0	+	0	0	+	Resected		....
14	Cough, pain	+	+	+	0	0	Resected	+	....
15	Pain	+	+	+	0	0	Resected	+	....
16	Hemoptysis	+	+	+	0	+	Not resectable		....
17	Cough, pain	+	+	+	0	0	Resected		....
18	Pain	0	+	+	....	0	Not resectable	+	+
19	Cough	+	+	+	0	....	Not resectable	+	....
20	0	0	+	+	0	+	Resected		....
21	Cough	+	+	0	....	0	....		....
22	Cough	0	+	+	+	+	....		....

* + indicates present; 0, absent; ...., not done.

more than 18 months. Seventeen patients, therefore, had joint symptoms as the first or only evidence of disease. Three patients had chest symptoms before joint symptoms and two had no joint symptoms.

Eight patients had no chest symptoms and twelve had no abnormalities noted on physical examination of the chest (Table 3). Five patients had neither chest symptoms nor abnormal physical findings on chest examination. Radiographic examinations of the chest were abnormal in all patients, however. Nevertheless, it is noteworthy that the chest x-ray films were not considered suggestive of malignant disease in 3 of the 20 patients with neoplasms. The commonest chest symptom was cough, which occurred in 10 patients; the next was pain which was usually pleuritic in nature and present in 6 patients; hemoptysis occurred in 2.

Bronchoscopy yielded the diagnosis in only 2 of the 15 patients with carcinoma who were subjected to this procedure. On the other hand, an equal number of the group with neoplasms had examination of the sputum for malignant cells, and nine showed such cells. These observations emphasize the peripheral nature of the tumors as observed on roentgenograms. Fifteen of the patients had chest surgical procedures; fourteen, thoracotomies, and one, a punch biopsy of the lesion. In nine of these the diagnosis of neoplasm was first established at the time of surgery.

TABLE 4.—*Response to Surgical Removal of Lung Lesion* *

Case	Resection: Symptoms	Resection: Radiographic Changes, Bones	Cortisone	Corticotropin
1	+	+	+	0
4	+	+	+	..
7	+	+	..	..
10	Not operated on	..	+	..
11	+	..	+	..
12	+	..	..	..
13	+	..	..	..
14	+	..	..	..
15	+	..	..	..
16	Not resectable	..	+	..
19	Not resectable	..	+	..
20	+	..	..	..

* + indicates improved; 0, no response; .., not followed or not treated.

Of the 14 tumors in patients who had thoracotomies, 9 were resectable (Table 4). All who had the primary tumor resected showed dramatic relief of joint and extremity symptoms, with pain relief occurring in 24 hours or less. There was diminution of

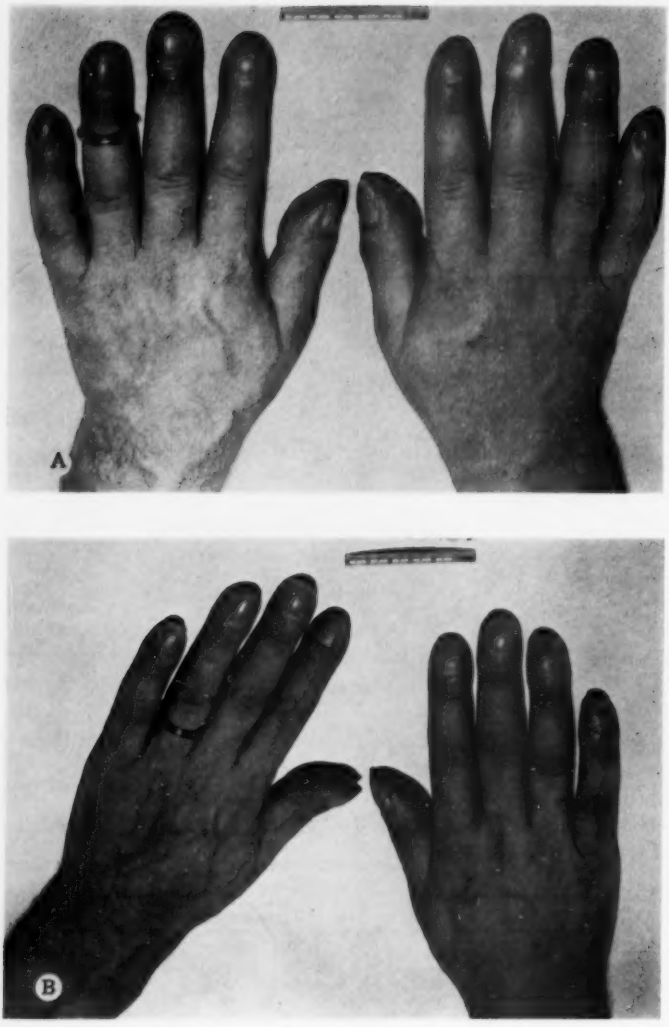

Fig. 4 (Case 13).—Photographs of hands. *A* shows the hands before surgery, and *B*, the two weeks following. He had been unable to wear the wedding ring for several weeks. The day preceding surgery, the right hand displaced 475 cc. of water; two days later, 430 cc., and two weeks later, 415 cc. Three days after surgery all pain had disappeared and the erythema of the tips of the fingers had faded.

swelling, evident very rapidly, disappearance of effusions, and decrease in bone tenderness (Fig. 4). Three patients who had resections were followed with repeated x-ray films of the bones for many months, and all showed a decrease in the x-ray changes, although none returned to normal. The patients whose tumors were inoperable or nonresectable had an inexorable progression of the joint disorder. Six patients who received one or more courses of cortisone were substantially relieved of joint pain. This improvement accentuated the confusion with rheumatoid arthritis in a few. The response to cortisone also suggests that it may be a useful palliative procedure where the operative treatment of the tumor fails.

The hematologic studies were as anticipated; the white blood cell count was usually normal, the hemoglobin was usually moderately reduced, and the erythrocyte sedimentation rate was rapid (Table 5). Serum calcium and phosphorus were normal, with the exception of one slightly high calcium

TABLE 5.—*Laboratory Studies*

Case	White Blood Cells	Hemoglobin, Gm./100Cc.	Erythrocyte Sedimentation Rate, Mm./Hr.	Calcium	Phosphorus	Alkaline Phosphatase*		Liver Function	17-Ketosteroids, Mg./24 Hr.	Follicle-Stimulating Hormone, M.U./24 Hr.	Glucose Tolerance	Insulin Tolerance	Adrenal Function
1	Normal	13.8	93					Sulfobromophthalein 17%	--	--------	----	--------	------
2	Normal	11.5	80					Normal		96-192	----	--------	------
3	Increased	12.0	20	9.6	4.1	19	KA	Cephalin flocculation 3+	7.1	High	----	Hypoglycemia; unresponsiveness	Robinson Kepler Power test + 1st & 2d part
4	Normal	10.1	104	8.2	4.3	10	KA	Normal		6-12			
5	Normal	11.4	69					Normal	--	--------	----	--------	Diagnostic of Addison's disease
6	Normal	11	90	9.1	4.2	13.5	KA	Normal	7.5	36-72	----	--------	------
7	Normal	14	11			11	KA	Sulfobromophthalein 14.5%	--	--------	----	--------	------
8	Normal	12.6	41										
9	Normal	13.8	62										
10	Normal	11	87						----	--------	Diabetic	--------	Robinson Kepler Power test + 1st part — 2d part; Thorn test, normal
11	Normal	14	40	8.7	4.4	0.5	B	Normal	8.3	6.5	Diabetic	Normal	
12	Normal	11.8	36	12.8		7.6	B	Cephalin flocculation 3+	3.9	6.5-13.0	----	--------	Robinson Kepler Power test + 1st part, equivocal 2d part; Thorn test, normal
13	Normal	12.2	--	9.4	5.1	31	B	Normal	----	Normal	----	--------	
14	Normal	11.3	37	9.5	2.9	13	KA	Normal					Thorn test, normal
15	Normal	14.4	20	10.0	3.5	16	KA	Normal	----	--------	High fasting	--------	------
16	Normal	13.2	--										
17	Normal	10.8	100					Cephalin flocculation 3+, Sulfobromophthalein, 10%	----	--------	----	--------	------
18	Normal	13	34	8.0	4.1	8.7	B	Normal	8.0	96-192	Equivocal	--------	Robinson Kepler Power test + 1st part, equivocal 2d part
19	Normal	9.4	--								Diabetic		Thorn test normal; Robinson Kepler Power test + 1st part, equivocal 2d
20	Normal	9.6	--	10	4.3	1.9	B	Normal					
21	Normal	12.5	44			1.4	B	Cephalin flocculation 3+	----	--------	----	--------	------
22	Normal	12.5	40			21	B	Normal	.7	13-52	----	--------	------

*KA indicates King-Armstrong units; B, Bodansky units.

determination. The alkaline phosphatase was slightly elevated in 5 of 13 patients.

In 6 of 17 patients one or more liver function tests were abnormal. Of the 16 men who had liver function studies, 8 also had gynecomastia. There was no correlation between the presence of gynecomastia and the finding of abnormal liver function, since two of the eight with gynecomastia had liver abnormalities and three of the eight without gynecomastia had liver abnormalities. In no patient was overt liver disease demonstrated.

A few studies of endocrine function were performed. Case 5 had Addison's disease due to replacement of the adrenals by Hodgkin's disease. The Robinson-Power-Kepler water test was performed in five other patients, and in all the morning specimens had a smaller volume than the night specimens. The second part of the test was negative in one, positive in one, and equivocal in three. The Thorn test was normal in the four patients. Five patients had glucose tolerance, and a diabetic type test was found in three. One other patient had a high fasting glucose level. The 17-ketosteroid excretion was determined in six patients and was normal in four and moderately reduced in two patients. The excretion of follicle-stimulating hormone was measured in nine patients and was normal in three, slightly elevated in three, and slightly decreased in three. There was no correlation with these minimal changes in follicle-stimulating hormone and the presence or absence of gynecomastia. No clear-cut endocrine abnormality except in Case 5 was discovered. In the other patients, the changes which were observed might be related to inanition, which was frequent.

Comment

Arthralgia is frequently mentioned as a prominent symptom of hypertrophic osteoarthropathy and may be the earliest warning of carcinoma of the lung. There are numerous reports [14] of pulmonary neoplasm masquerading for years as arthritis before the underlying nature of the disease process was recognized. Craig,[15] in 1937, reported four cases of carcinoma of the lung associated with hypertrophic osteoarthropathy and stressed the importance of recognizing arthritis as a possible early symptom of pulmonary neoplasm. Three of his cases were first diagnosed as rheumatoid arthritis and one as acromegaly. Berg,[16] in a recent review of the literature, reported 15 cases of pulmonary neoplasm which had presented symptoms of bone pain or arthralgia. He added five similar cases of his own. Holmes et al.[17] reported seven such cases. In five of their cases, the joint pains preceded the clubbing. Three of their cases were treated for arthritis for several months before recognition of the pulmonary neoplasm. Vogl et al,[7] and Semple and McCluskie [10] have stressed this relationship. The patients seen by us emphasize the association of hypertrophic osteoarthropathy and neoplasm of the lung, the frequent appearance of joint symptoms before chest symptoms, and the infrequent recognition of the significance of the syndrome. Ray and Fisher [18] noted that when hypertrophic osteoarthropathy developed slowly in cases with pulmonary suppuration, the arthritic symptoms were not prominent, but that in their cases of carcinoma of the lung the arthritic symptoms were severe. This was also true in the patients in our series.

One of the most interesting aspects of the relationship between pulmonary neoplasia and hypertrophic osteoarthropathy is the striking relief of bone and joint pains within hours or days after the resection of the primary tumor, even if metastases were present. The clubbing often disappeared, and joint changes regressed. Subsequent x-rays have shown return of the bones to normal in six to nine months.[19,20]

Gynecomastia, as noted in this series, has frequently been seen in association with pulmonary tumors and hypertrophic osteoarthropathy.[17,19,21] Gynecomastia may be present with lung tumors in the absence of osteoarthropathy. One of our patients had

a bilateral mastectomy for gynecomastia before the presence of pulmonary carcinoma was demonstrated. A roentgenogram of the chest should therefore be part of the investigation of a patient with gynecomastia.

Clubbing of the fingers in association with hypertrophic osteoarthropathy is usually asymptomatic.[12] The first sign noted clinically is increased fluctuation of the nail bed, followed by thickening of the fibroelastic tissue of the base of the nail, which results in the filling out of the angle between the nail and the basal tissues. Alterations in the curvature of the nails next occurs. Hypertrophic osteoarthropathy has been said always to be associated with clubbing of the fingers.[21] However, in a patient who developed both conditions within one month, definite x-ray changes in the bone preceded the clubbing of the fingers,[23] and one of our group showed no clubbing.

The pathologic process in hypertrophic osteoarthropathy is essentially a chronic proliferative subperiosteal osteitis with successive layers of new-bone formation.[24] However, by means of actual volume measurements,[12] increased blood flow in the venous plexuses was found to be a factor only in cases of congenital heart disease with cyanosis.

Hypertrophic osteoarthropathy has been reported in dogs with pulmonary tuberculosis, pulmonary suppuration, and carcinoma of the lung. Mendlowitz and Leslie[24] reported an experimental production of hypertrophic osteoarthropathy in a dog by anastomosing the pulmonary artery and the left auricle.

There may be a relationship between the location of the carcinoma and the development of hypertrophic osteoarthropathy. Ray and Fisher[18] reported 139 cases of carcinoma of the lung, of which 14 had hypertrophic osteoarthropathy. In 13 of the 14 the tumor was peripheral. They found no apparent relationship between tumor type or tumor size and the development of hypertrophic osteoathropathy. Although infection was a prominent feature in 57 of their cases of carcinoma of the lung, none of the cases of hypertrophic osteoarthropathy had significant pulmonary infection. They cited several other examples of the relationship of hypertrophic osteoarthropathy to peripheral carcinoma, including six cases of Pattison, Beck, and Miller,[25] five of which were peripheral and one in a secondary bronchus. They stated that two of Fried's four cases were peripheral. Of Holmes'[17] seven cases, five were peripheral. Sixteen of twenty-four cases of localized fibrous mesothelioma of the pleura[27] had joint symptoms, and eleven had finger clubbing. The authors reported prompt relief of these symptoms after surgery.

Hypertrophic osteoarthropathy has been reported with carcinoma of the lung with metastases to the pituitary[28] or the adrenals. However, hypertrophic osteoarthropathy occurs without metastatic spread of the tumors, and reports of hypertrophic osteoarthropathy with metastases to these glands have been infrequent. Only one of our group had involvement by tumor of the adrenals, and none, of the pituitary gland.

In considering the relationship between carcinoma of the lung and hypertrophic osteoarthropathy, a most interesting question presents itself: Why should a growth in the periphery of the lung produce the reversible systemic changes of hypertrophic osteoarthropathy? When one considers that there may be no relationship to tumor type or size and that the relief of symptoms can occur even after a palliative resection, the problem becomes even more fascinating. From the nature of the generalized changes produced, perhaps the growth has disturbed some primary metabolic function of the lung itself. The other alternative, hormone production by the tumor itself, seems unlikely, since the syndrome occurs with many types of benign and malignant tumors, primary or metastatic, and even with infectious processes.

The tests for endocrine dysfunction which we have performed have been unrevealing. Semple and McCluskie[19] have considered

the possibility of an autonomic pulmonary-systemic vascular reflex. They believe that such a theory could explain the relief afforded by tumor removal, pulmonary artery ligation, hilum denervation, and vagus resection.[20] For the present, the pathogenesis of hypertrophic osteoarthropathy remains obscure. Recent reports of neuropathies and dermatomyositis secondary to tumors, particularly those of the lung, indicate that other generalized and possibly related phenomena may occur in response to a local growth.[9]

Summary

Pulmonary neoplasms are the chief cause of hypertrophic osteoarthropathy in this part of the world. Of 22 patients with this syndrome, 20 had malignant lesions of the lung. Dramatic relief of the joint symptoms followed removal of the tumor.

The pathogenesis of osteoarthropathy is still obscure. Frequently patients with hypertrophic osteoarthropathy are mistakenly treated for arthritis for years before a lung tumor is finally discovered.

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The Nature of Man's Adaptation to His Total Environment and the Relation of This to Illness

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The modern investigation of how man's adaptation to his environment affects his health dates from Claude Bernard. During the succeeding century, there has been a continued interest in the field in which Bernard pioneered, and the number of those working in the area has increased steadily. Information has been gathered from sources as diverse as neurology, endocrinology, cultural anthropology, and the statistics of time series,[1] each part of which has contributed to general concepts which could not have been constructed even so recently as 10 years ago. The purpose of the present paper is to describe some of the findings from a study carried out by us and our colleagues,* which is concerned with the distribution of illness in three population groups, the influence of environmental factors upon this, and its significance in the light of our knowledge derived from laboratory experiments.

Methods

Over the past five years, members of our group at the New York Hospital-Cornell Medical Center have carried out investigations of the distribution of illness in three homogeneous population groups totalling 2924 persons (Table 1). The first of these groups was made up of 1297 adult women, all of whom were healthy as ascertained by physical examination and medical history at age 14 to 18. These women were of second generation Irish and Italian descent, of upper-lower-class background (Warner and Lunt[8]) with grammar-school educations. They had spent their lives in a large city with uniform and adequate sanitation, where they mingled freely with the general population and had ample opportunity for exposure to the pathogenic agents present. From the time of their initial examination onward for periods as long as 30 years, they had all been constantly employed in the same unskilled but relatively well-paid, nonhazardous work, for a corporation which maintained complete records of their health and attendance. These records included a description of every illness causing absence from work, periodic physical examinations, reports from private physicians, and diagnostic reports from hospital admissions.

In this group of 1297 women, there were 336 who had been continuously employed for 20 years or more. The distribution of illness in the entire group was studied, but special attention was also given to the 336 with long service. From this long-service group there were selected the 20 women with the greatest number of total days of sickness disability and the 20 with the smallest number. These women were examined individually, and extensive histories were obtained from them during interviews lasting several hours; extensive personal histories were obtained also. A similar procedure was followed with more than 60 women selected at random from among those having intermediate amounts of illness.

The second group studied was made up of 1527 adult men employed by the same corporation. This group was homogeneous with regard to all the factors described for the women, but was different in the following features: Its members were largely third-generation Americans, primarily of Irish and Italian descent, but including approximately 25% of German or English protestant descent. They were of lower-middle-class back-

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TABLE 1.—*Characteristics of the Three Groups*

	Group I	Group II	Group III
1. Total number studied	1,297	1,527	100
2. Number studied intensively	336	279	100
3. Age	17–50	17–55	19–72
4. Sex	Women	Men	Men and women
5. Cultural background	2d generation Irish and Italian American	Mixed indigenous American	Chinese
6. Socioeconomic background	Upper lower class	Lower middle class	Upper class
7. Education	Grammar school	High school	College
8. Occupation	Unskilled white-collar	Skilled workmen	Graduate students, professional men
9. Lifetime environment	Metropolitan New York	Metropolitan New York	Various parts of China (later United States)
10. Sanitation of general surroundings	Generally high	Generally high	Generally very low
11. Exposure to pathogens and trauma	Low	Moderate	High
12. Physical deprivations, pressures, and dislocations	Few	Few	Many
13. Social dislocations and situations of uncertainty	Few	Few	Many

ground, with high school educations, and were employed as skilled workmen. Similar records were available on these men, of whom 279 having more than 20 years of unbroken service were selected at random for intensive study. The investigative procedure for this group was similar to that used with the group of women.

The third group was made up of 100 adult Chinese men and women, now mostly in the fourth decade of life. These people were all born in China and came to the United States approximately 10 years before as graduate students. Because of the changed political situation in China they have been unable to return and have remained in this country in a situation of uncertainty since that time. They were all, of course, of Chinese descent, although they came from various parts of China. They came largely from well-to-do families of established positions in their communities. Almost all of them had completed college, and most had higher degrees. In general, they had looked forward to careers as scholars, administrators, government officials, and members of various professions.

This group also was unselected with regard to health. Each member of the group was studied for 16 hours in the following manner: Four hours was spent in obtaining a complete medical history and physical evaluation, with diagnostic tests; this was carried out by a physician; four hours was spent in interviews with a cultural anthropologist (supplemented, in some instances, by a sociologist) who obtained a biographical statement, as well as other information relating to the position of the informant in relation to his social environment, both in China and the United States. Four hours was spent with a psychiatrist, who focused upon an evaluation of the personality structure of the informant, his perception of his life experiences, and an estimate of their meaning to him. Four hours was spent with a clinical psychologist, who utilized a battery of tests which included the Wechsler-Bellevue Intelligence Scale, Form I, the Rorschach, the Lowenfeld Mosaic, a Projective Questionnaire, Sacks Sentence Completions, Thurstone Temperament Scale, and Human Figure Drawings. The Thematic Apperception Test was administered to about 30 of the informants also. Each of these observers studied the informants independently and gathered his data independently; later the informants were discussed at conferences of the four disciplines.

There was, of course, no independent record of the illnesses which these Chinese had experienced, and it was necessary to use their own memories in order to obtain this information. Experience with the two American groups, in which medical histories given from memory were compared with medical records obtained independently, showed that statements about major illnesses, as described from memory, were in general remarkably accurate and that estimates of minor illnesses were close enough to provide a reliable general indication of the informants' state of health with regard to these. Evidence obtained from the description of illness given in each Chinese informant's medical history, evaluated in the light of the assessments made by the psychiatrists and psychologists, was also used to evaluate the data. It is our opinion that the health of these Chinese informants, as measured by our methods, is a reliable reflection of their true state of health.

Each of these groups was selected in part because its members had shared an essentially equal exposure to the various aspects of a common physical environment and an essentially equal opportunity to encounter the various external causative agents which are known to be relevant to the development of disease. Each of the American groups was made up of steadily employed people with adequate incomes, living in adequate housing, with adequate and varied diets, and mingling intimately with members of a large metropolitan population. The Chinese had been irregularly employed and had experienced fluctuations in their income, housing, and diets. All of them had been

exposed to the inadequate sanitation and flourishing pathogenic agents of China. They had all experienced physical dislocation and physical hardships during the wars and social upheavals which have occurred in China in the last three decades, and for the group as a whole these experiences were essentially equal.

Results

1. The distribution of illness among the members of each of these three groups was not a random distribution. A significant proportion of each group had experienced far more than the amount of illness to be expected if chance alone were the determining factor. The distribution curves for the three groups were remarkably similar. That for the group of American men is shown in Figure 1. This is not a Poisson † distribution, as one might expect if chance were the sole determining factor.[6] The distribution most resembles the negative binominal distribution that occurs in groups when the members of the group have different "risks" (or, in nonstatistical terms, "likelihoods") of becoming ill. This point has been examined statistically with great care, especially among the group of American men. It is quite clear that, in spite of the homogeneity of each of these groups with regard to the characteristics of its members and of the physical environment shared by them, some members of each group had a greater "risk" of becoming ill than others.

This difference in risk was not limited to one point in time but clearly extended over a period of years. For example, the number of illnesses experienced by each man in the American group during the first 5 years of the observation period showed a positive correlation with the number of

† The "Poisson" distribution is a mathematical description of the distribution of rare events when each event is independent of the others.

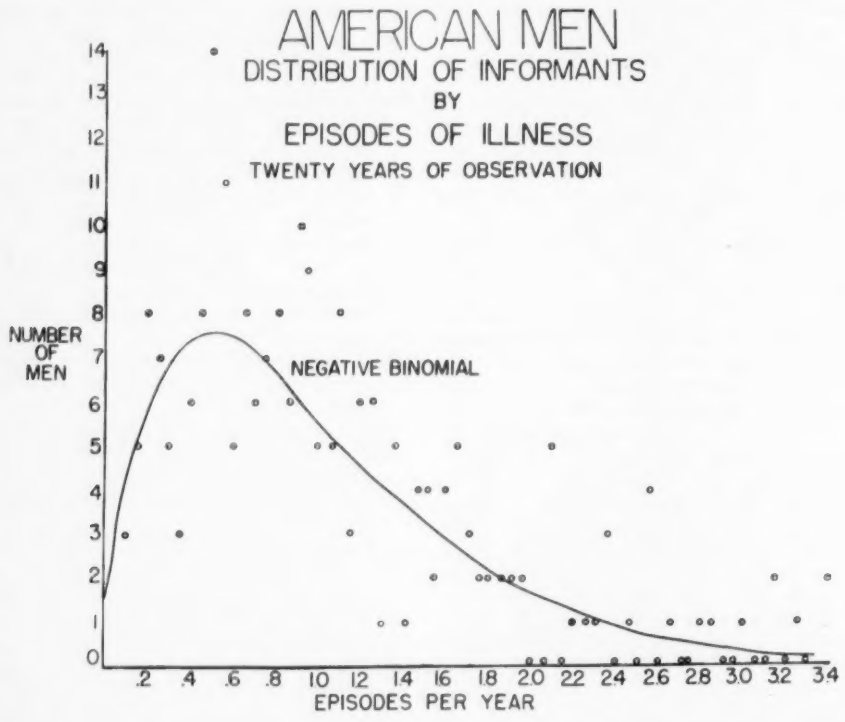

Figure 1

episodes of illness experienced during the subsequent 15 years. The findings are similar in the other two groups.

Our inference from these findings is that marked differences in susceptibility to illness occur among the members of the general population, that these differences last for a number of years, and that they are related to some factor (or factors) which operate similarly in all of these groups.

2. The nature of the illnesses experienced groups was examined. In every group it was found that those members having the greater number of illnesses experienced a by the individual members of each of these wide variety of illnesses, both major and minor, in a number of body systems. There was a positive correlation between the number of episodes of illness experienced by each person and the number of body systems involved in these illnesses. Figure 2, taken from the study of the Chinese, illustrates this. It was common to find that one type of illness, such as upper respiratory infections, gastrointestinal disturbances, migraine headaches, or recurrent episodes of anxiety, might appear as a recurring feature in the health history of a person, but no person was found who had a great many illnesses limited to one or even to two or three body systems. All of those who had many illnesses involving one body system usually had other illnesses, and some serious illnesses, involving other body systems. Furthermore, there was a general parallelism between the number of "major" illnesses and the number of "minor" illnesses which one man experienced. As a group, those having the greater number of minor illnesses also had the greater number of major illnesses, and these major illnesses usually involved the body systems which were most frequently involved in the minor illnesses. Figure 3, taken from the group of American men, illustrates this.

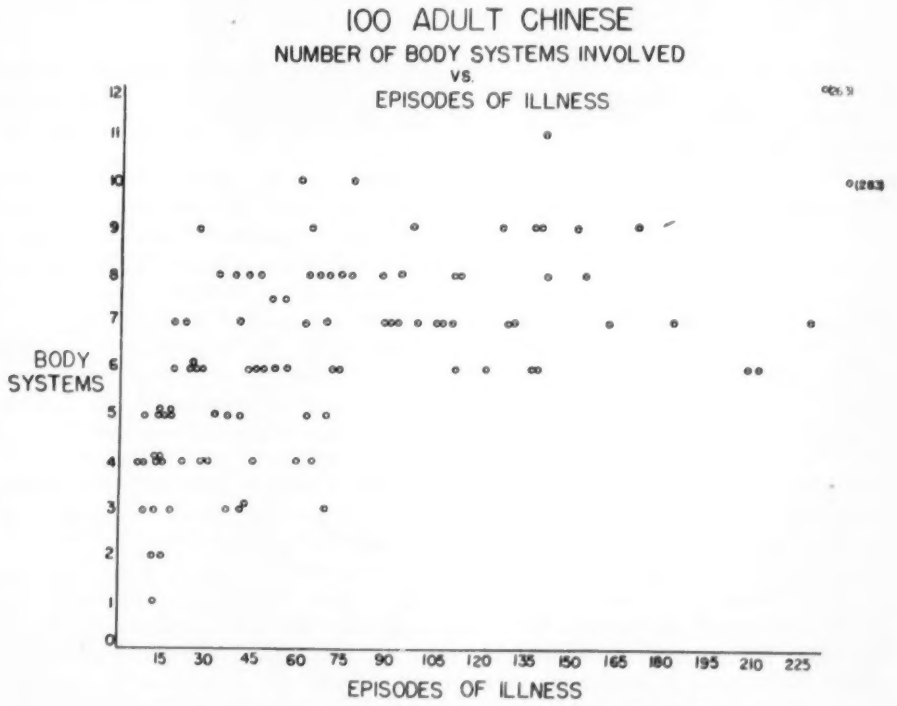

Fig. 2.—Study of 100 adult Chinese; $r=0.65$, $r^2=0.422$, $P<0.01$.

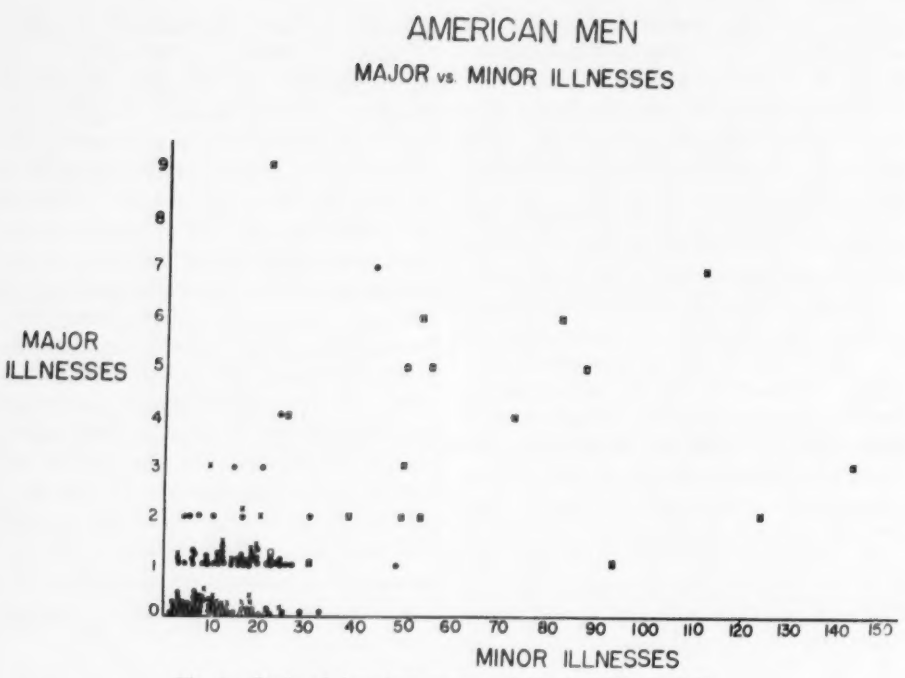

Fig. 3.—Study of American men; $r=0.40$, $r^2=0.160$, $P<0.01$.

There was a similar relationship between the so-called "bodily illnesses" and disturbances of mood, thought, and behavior; that is to say, those people who had the greater number of bodily illnesses, regardless of their nature and regardless of their etiology, were the ones who experienced the greater number of disturbances of mood, thought, and behavior (Fig. 4, from the Chinese study). For example, not uncommonly, persons were seen with recurrent episodes of anxiety, depression, chronic obsessive and compulsive symptoms, or character disturbances; symptomatology of this type, with exacerbations and remissions, might predominate in their illness patterns throughout life. But such people, as a group, also had more bodily illnesses of all types than were found among those who had few or no disturbances of mood, thought, or behavior. This can be put in other terms by saying that, in all three of the groups studied, there was a parallelism between the occurrence of psychoneuroses and psychoses and the occurrence of bodily illnesses. There was a similar relationship between illnesses and accidents (Fig. 5, American men).

Thus those who had the greater "risk" of becoming ill, and who therefore experienced the greater number of illnesses, showed an increased susceptibility to illness in general. (Table 2 is an example. This American woman was selected for study solely on the basis of the fact that she had had 1041 days of disability in 35 years.) Whatever factors were associated with the increased risk of illness affected susceptibility to all forms of illness. As a group, those who became ill most frequently were more likely to develop severe illnesses than those who became ill less frequently.

Our general inference from these findings is that "illness" is a state of the total organism, that when a human moves from a state of "health" into a state of "illness," the "illness" is likely to be manifested by a variety of syndromes appearing concur-

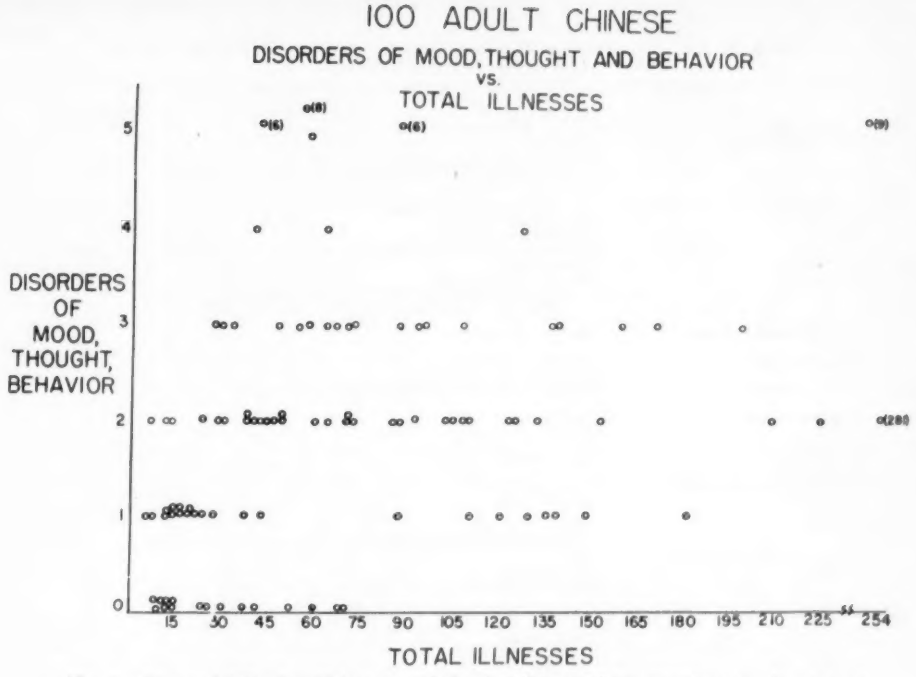

Fig. 4.—Study of 100 adult Chinese; $r=0.45$, $r^2=0.202$, $P<0.01$. For those having one or more episodes of disturbances of mood, thought, and behavior, $r=0.82$, $r^2=0.672$, $P<0.01$.

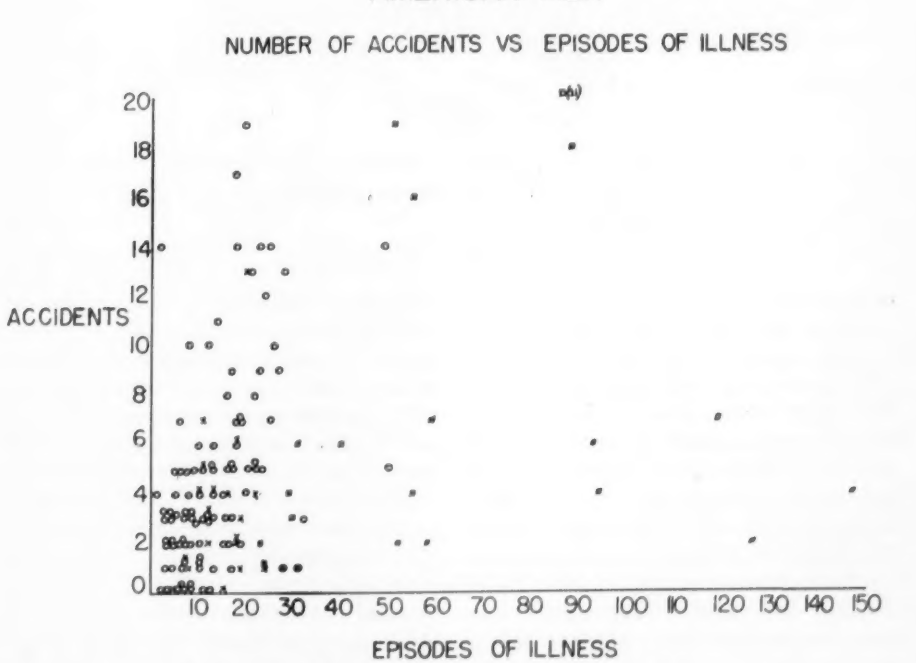

Fig. 5.—Study of American men; $r=0.5$, $r^2=0.25$, $P<0.01$.

TABLE 2.—*An "Ill" American Working Woman: Illnesses Experienced from Age Sixteen to Age Fifty-One*

"Body System"	Syndrome		Episodes of Disability
1. Respiratory system	Influenza;		1
	pertussis;		1
	minor upper respiratory infections;	(Approx.)	44
	severe tonsillitis		2
2. Gastrointestinal system	Cholecystitis and cholelithiasis;		2
	diaphragmatic hernia;		5
	duodenal diverticulum;		0
	postoperative biliary symptoms;		4
	mucous colitis;		4
	infectious gastroenteritis		3
	(chronic, nondisabling constipation, low abdominal pain, "gas," and nausea, present for many years also)		
3. Cardiovascular system	Essential hypertension		0
4. Genital system	Myomata of uterus;		1
	dysmenorrhea (chronic);		
	postmenopausal flushes, severe		
5. Urinary system	Pyelonephritis;		1
	cystitis		1
6. Blood	Hypochromic anemia		
7. Musculoskeletal system	"Low back pain";		4
	osteoarthritis		1
8. Head	Vascular headaches		2
	(nondisabling headaches occurred about once a month)		
9. Ears	Otitis media;		2
	Ménière's syndrome		1
10. Eyes	Conjunctivitis		1
11. Teeth	Dental caries		3
	(total extractions)		
12. Skin	Urticaria;		2
	cellulitis		1
13. Breast	Fibroma		1
14. Metabolic	Obesity		
15. Mood, thought, behavior	Moderately severe depressions;		3
	anxiety-tension states		5
	(symptoms of anxiety, tension, depression chronically present)		
Accidents	Contusions;		8
	lacerations;		3
	sprains		1
Operations	1. Cholecystectomy		
	2. Hysterectomy and oophorectomy		
	3. Excision of fibroma of breast		
	4. Total dental extractions		

Summary

Total days disabled	1041
Disabling episodes of illness	95
"Major" illnesses	9
Disabling disturbances of mood, thought, and behavior	8
"Body systems" involved	15
Accidents	12
Operations	4

rently or consecutively, their nature being dependent upon the various factors acting upon the organism at that time.

3. In order to ascertain the circumstances under which illness occurs, the sickness patterns of members of each group were studied intensively. Each illness episode was carefully located with regard to the time when it occurred in the life of the person. Among the subjects in all three groups, those having many illnesses as well as those having relatively few, it was found that illnesses were not scattered in a random fashion throughout their lives. Instead, illnesses usually appeared in clusters (Fig. 6). There would be periods of years in the life of a person when he was relatively healthy, and other periods of years during which he would have a number of episodes of illness. One form of illness might predominate in such a cluster, but it was rare to find that one form alone appeared. Usually a cluster was made up of a variety of illnesses involving several body systems, running concurrently or consecutively, over a period of years and followed by a num-

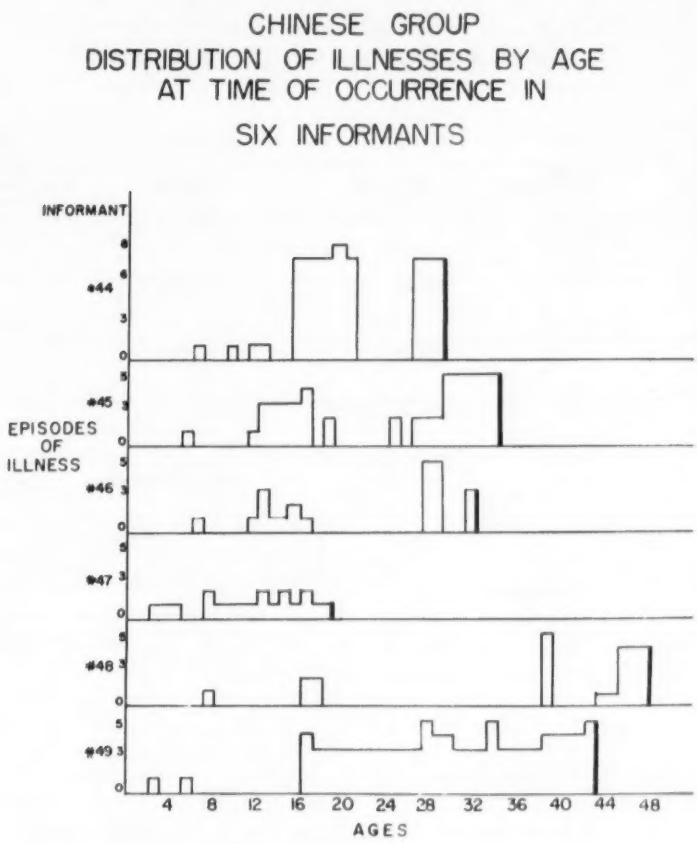

Figure 6

ber of years of relatively good health during which there were few illnesses of any sort (Fig. 7).

Such clusters were usually of 5 or 10 years' duration. Those seen in the American groups were perhaps somewhat longer than those seen in the Chinese. This appeared to explain why there was a positive correlation between the number of episodes of illness occurring in the informants during one period of years and that occurring during a subsequent period of years; the duration of these clusters was such that they usually overlapped the two periods which were being compared. However, it was not common to find anyone who had persistent and recurrent illnesses throughout his entire life; nor was it common to find others who had had essentially no illness at any time in their lives. Even among those having the fewest episodes of illness, these illnesses often appeared in clusters covering a relatively few years.

Even though the three population groups were selected because they had shared similar physical and social environments and some similar life experiences, these factors were focussed upon intensively in the study of selected persons. Differences in exposure to physical hardships, dietary differences, differences in exposure to infectious or toxic agents, and differences in general physical life experiences did not appear to account for the differences in susceptibility to illness. In general, the lives of the most healthy and the lives of the least healthy

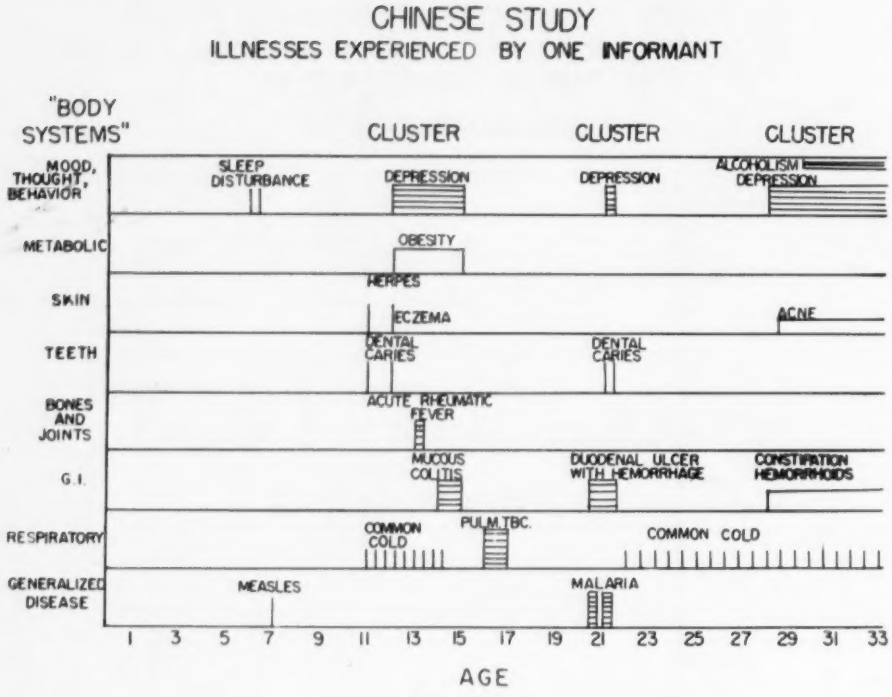

Figure 7

members of each group were similar with regard to these factors.

The life histories of the informants were examined in an attempt to see what correlation there was between the objective facts of the interpersonal and social adaptations which they had found it necessary to make and the occurrence of their illnesses. Here there was a difference, but it was by no means absolute. A large proportion of the most frequently ill members of the two American groups had been reared in families in which there was dissension and conflict between the parents, with hostile and rejecting attitudes on the part of one or both toward the children, divorces, emotional deprivation, and unusual restrictions or demands placed upon the offspring. Relatively few of the healthiest members of these groups had experienced any of this to a significant degree. The data from the Chinese group, which is still being evaluated, appear to show the same things.

However, there were demonstrably healthy people in all three groups who had been reared in family settings in which there was a marked degree of dissension, emotional deprivation, hostility, and restriction; furthermore, some of the people who during their adult lives were among the sickest in each group had been relatively healthy during the period of their apparently adverse experiences in childhood. Thus it seems that such "objectively" adverse childhood experiences are positively correlated with adult ill health; but they cannot be invoked as a satisfactory explanation for predisposition to illness in adult life, including the disturbances of mood, thought, and behavior. Table 3, taken from the study of the American women, illustrates this.

Similarly, a study was made of the association between the "objective" aspects of adult interpersonal relations and social demands and the occurrence of illness. It was found that during their adult lives a large

TABLE 3.—*American Working Women: Summary of the Independently Observable Facts of the Background and Life Situation of the Most Healthy and the Least Healthy of the Members of the Group*

	"Well Group"		"Ill Group"	
1. Heredity	No major difference			
Familial diseases	None		None	
2. Health of parents and siblings	No major difference			
3. Longevity of parents				
Fathers	51.7 Yr.		54.5 Yr.	
Mothers	60.4 Yr.		58.5 Yr.	
4. Health during childhood	No major difference			
5. Economic and cultural background in childhood	No major difference			
6. Exposure to infection and trauma	No evident difference			
7. Constitutional factors detectable by physical examination or routine diagnostic tests	No evident difference			
8. Psychosocial environment in childhood				
A. Without undue demands, conflicts, or deprivations	15		6	
B. Heavy demands, frequent conflicts, and deprivations; insecurity	5		14	
9. Psychosocial environment in adult life				
A. Without undue demands, conflicts, or deprivations	12		0	
B. Heavy demands, frequent conflicts, and deprivations; insecurity	8		20	
10. Marital relationship				
Single	13		6	
Married, now or formerly	7		14	
Instances of marital incompatibility		3		15
Total number of separations or divorces		2		8
Total number of children		2		16
11. Occupational satisfaction				
Satisfied	20		3	
Dissatisfied	0		17	

proportion of the "sickest" members of the two American groups had experienced divorces; separations; conflicts with parents, siblings, husbands, and wives; uncongenial living and working arrangements, and the like and that relatively few of the healthiest members of these groups had had comparable experiences. The data from the Chinese study appears to be consistent with this. But again, this difference was not absolute. While it could be shown that a great many of the observed clusters of illness occurred during periods of "objective," demonstrable interpersonal difficulties and conflicting social demands, it could also be shown that such situations not infrequently occurred both in the healthiest and unhealthiest members of all of the groups without being associated with any significant symptomatic disturbances.

This was in part a matter of degree. Any severe disruption of interpersonal relationships and any marked change in the demands of the social situation was almost invariably found to be associated with some minor change in mood, thought, and behavior and some minor disturbances of bodily processes; but in many instances, even though the disruption in the social or interpersonal life of the informant was objectively a major one, the symptomatology associated with this could not be considered to be of sufficient magnitude or duration to represent an "illness." On the other hand, some objectively minor disruptions in the life of a person might be temporally associated with a major disturbance of mood, thought, and behavior, or major bodily illness, which could not be explained on the basis of the interposition of any external causative agent. Thus, it is clear that, while there is a positive association between the occurrence of illness and the occurrence of objective changes in interpersonal relations and in the demands of social situations, and probably a significant one, this cannot be invoked as an adequate explanation of the changes in the amount of illness exhibited by an individual informant from time to time.

If one relies solely upon measurements which can be confirmed by independent observers and by external records, one can say only that adverse childhood experiences, difficulties in adult interpersonal relations, and heavy demands from the social environment are positively associated with an increased susceptibility to illness of all forms, and from this data alone it seems very likely that they have an important effect upon human susceptibility to illness in general.

4. However, it is believed that the individual man does not react to the events and situations in his social environment simply

as they appear "objectively" to other people. It is, of course, true that men in general have similar needs for protection, dependency, human association, sexual fulfillment, and the like, even though these vary somewhat in degree from man to man. And it is also true that people sharing the same culture and the same social niche share many perceptions which are based upon their common learned behavior, their common experiences, and their shared values and aspirations. Because of this, one might expect that members of each of these homogeneous groups would find many disturbances of interpersonal relations and many types of social demands and deprivations, similarly difficult to cope with; therefore, one might expect that a majority of the members of each group who encountered certain types of difficult life experiences would have adverse reactions to these. Nevertheless, from what we know of man as a living system, there is no reason to expect that all people will react alike to the same situation.

It is the present belief that the reaction patterns of each person are in part determined by his constitutional make-up and in part by his life experiences, during which he "learns," in the broadest sense of the word, that some types of situations are peculiarly threatening to him and that others are peculiarly desirable. It is thought that each man reacts to each situation he encounters in life in terms of his total perception of the meaning of that situation, using the term "perception" as including both conscious and unconscious processes and using the word "situation" to mean not only the total configuration at that point in time, but also what this configuration symbolizes to him. If we accept these hypotheses, then, in order to ascertain how a man will react to the situations which he encounters, it is necessary to weigh each situation in terms of its peculiar meaning for him. This cannot be done simply by using evidence from outside observers. One must obtain from the person his own evaluation of the meaning of each situation, and the observer, himself, must also make inferences about the meaning of these situations, based upon his own knowledge of the informant's past experience and his estimation of the informant's needs, his drives, and his goals. In doing so, one is clearly introducing the possibility of personal bias on the part of the observer and on the part of the subject, himself. Nevertheless, some attempt must be made to make such an assessment, if one is to estimate the meaning to the person of events and situations in his social environment and the influence which his attempts to adapt to these have upon his health.

Such a careful assessment of the life histories and significant conflicts was carried out with all of the Chinese subjects and a selected sample of the two American groups, including both the most frequently ill and the least frequently ill. Although these evaluations were made by a number of observers, there was general agreement that in all of the cases studied clusters of illness often occurred during periods significantly stressful for the person, when he was striving to adapt to what were for him highly pertinent, conflicting, and often seriously threatening demands arising out of his relation to his total environmental constellation, as he perceived it (Fig. 8; the informant whose clusters are diagrammed in Fig. 7). It is our general inference, based upon our observations, that, in the individual members of all three groups, clusters of illness of all sorts most often occurred in periods when the subject was experiencing significant difficulty in his attempts to adapt to the conflicting demands of his total environment as related to his own needs.

5. The difference between the amount of illness experienced by the "most healthy" and "least healthy" members of each group might well be explained upon the basis of constitutional differences in general susceptibility to illness. Therefore, members of all three groups, including those having many illnesses as well as those having few, were

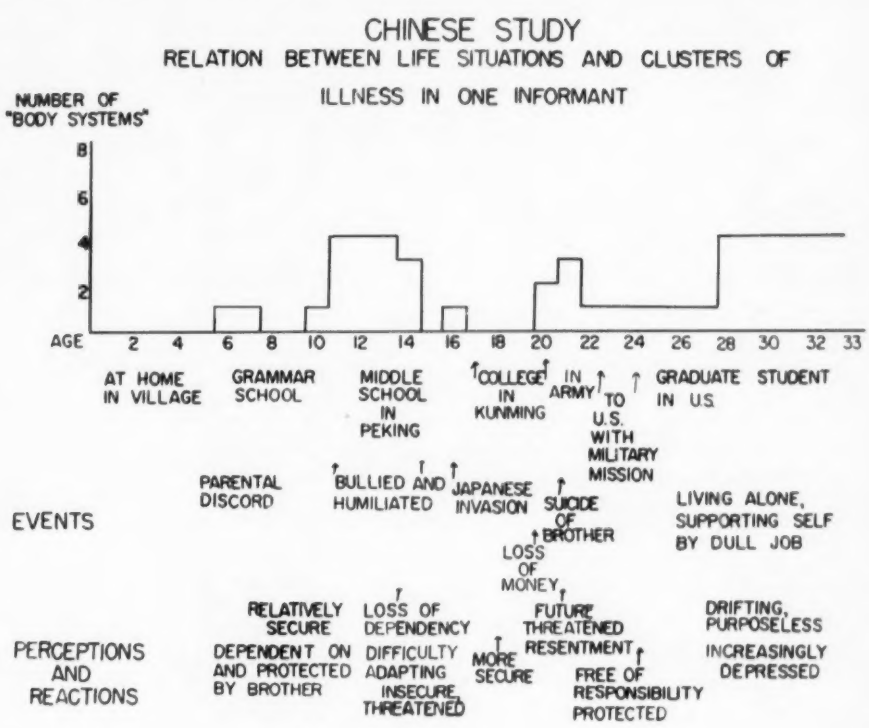

Figure 8

examined with regard to the occurrence of hereditary diseases, the health and longevity of their parents and siblings, and evidences of constitutional differences, such as anatomic abnormalities and metabolic defects, which might predispose to illness. Thus far, these have not been found to be significantly different in the healthiest informants as compared to the unhealthiest; but other constitutional factors not detectable by our methods may well have been present. They could explain why some people have much more illness during their lives than do others; but some additional factor would seem to be necessary in order to explain the "clustering" of illnesses. The most reasonable explanation for this is that the changing relationship between the informants and their external environment influenced their susceptibility to illness in general.

It is our inference that constitutional and hereditary differences in general susceptibility to illness were very likely present among the members of these groups; but we do not believe that they are responsible for the phenomenon of "clustering."

6. From these general observations upon the three groups, and from the characteristics of the healthiest and unhealthiest members, it appears that the members of these groups who were most healthy were people who were peculiarly well adapted to the particular life situation in which they found themselves, even though there might have been other life situations to which they could have adapted less well. The opposite was true of those who were most ill. From this we make the general inference that good health among our informants occurred when a person existed in a life situation which satisfied his own peculiar needs, however these might differ from those of the population in general, and that ill health occurred when a person existed in a life situation which placed excessive demands

upon him, or which failed to satisfy his own peculiar needs and aspirations.

Many of the least healthy did indeed appear to be people who had been so crippled by their early life experiences, or who possessed so many conflicting drives, that they could scarcely have adapted to any life situation; but some of the least healthy members of all three groups were persons of outstanding intelligence, superior education, and high standards of conduct, who were resolutely pursuing socially desirable goals in the face of repeated frustrations and overwhelming demands arising out of their life situations.

Some of the healthiest people were those who had spent their childhood in benign and secure surroundings and who appeared to have learned from their parents consistent patterns of mature behavior in dealing with life crises, and some of these people appeared to have dealt with their needs and the demands of their life situations with outstanding ability. But there were other healthy people who had encountered a variety of vicissitudes in their childhood environment and who seemed to have no special adaptive capabilities other than those peculiarly suited to the adult environment in which they found themselves, and there were still others who appeared to have maintained their health at the expense of markedly restricting their adult lives, establishing no heterosexual relationships, taking no responsibilities for the welfare of others, and exhibiting an almost pathological opportunism, shallowness of interpersonal relations, and callous indifference to the consequences of their decisions.

All of this we take to confirm the evidence, obtained from the life histories of many persons, that illness often occurs when a person perceives his life situation as peculiarly threatening to him, even though this life situation may not appear to be threatening to an outside observer, and that people who maintain good health in a setting of what are "objectively" difficult life situations do not usually perceive these situations as difficult.

Comment

From the physicochemical point of view, the individual man may be regarded as an independent living system, surrounded by an "environment" with which he constantly interrelates. The integrity of this system is ultimately dependent upon the maintenance of a dynamic equilibrium among the molecular configurations which make up the cells and upon the maintenance of the general integrity of the larger configurations which make up the various organ systems. Any disturbances of the human system which arise out of its relation to its environment are ultimately dependent upon the addition of energy to the system, the subtraction of energy from it, or the initiation of some process which alters the energy exchanges within it. Electric shock, heat, roentgen rays, and food are examples of environmental agents which disturb the system by adding energy to it; cold air and water are examples of agents which disturb the system by subtracting energy from it; and KCN, cyclopropane, and diptheria toxin are examples of agents which disturb the system by interfering with or altering energy transformations within it.

The great majority of toxic agents, congenital anomalies, vitamin deficiencies, and pathogenic micro-organisms act primarily by disturbing energy transformations within the system; but their action is not simply analagous to that of KCN. While most of them do to some extent directly disturb energy transformations and destroy cellular configurations, they also set in motion adaptive reactions on the part of the host which have a similar effect. A large proportion of the disturbance created by any toxic or infectious agent is created by the adaptive efforts of the host, itself, and this is true, in fact, even in the case of thermal and mechanical injuries. These agents act not only as sources of energy and of direct interference, they act also as "signals" which set in motion counteractions of the host which are both local and generalized and which are, to a certain extent, "nonspe-

cific"—a phenomenon to which Selye has applied the term, "nonspecific stress." In some disturbances, of which rheumatic fever and glomerulonephritis are prototypes, the "disease" consists almost entirely of the host's reaction, and the direct action of the agent is probably very small—although circulating antigen remains an important part of the mechanism.

Man is not limited to reacting to that part of his environment which impinges upon him directly. He shares with the higher animals organs of special sense and a central nervous system, which enable him to react to aspects of his environment which are separated from him both in space and in time. These aspects of the environment, which make up what we have called the "social environment," are no less "real" and "physical" than any other, and their division into a separate category is in part arbitrary, for the organism adapts to its environment as a whole, rather than to a part of it. However, there are some theoretical advantages to making this distinction, because there are certain special aspects of the mechanisms involved in adaptations to the "social environment."

The disturbances of the human system which arise out of its relation to its social milieu must arise through a mechanism somewhat different from that involved where there is a direct encounter with physical forces, infectious organisms, toxic agents, or dietary disturbances; for, as we have said, each of these latter acts directly to produce a disturbance in the human system, either through the application of energy from external sources or through directly altering or interfering with the normal energy transformations within the system itself, and the direct action of these agents can be regarded as a "cause" of any "disease" which may result. But man's social environment does not act upon him in any such manner; it is entirely "at a distance," and the person receives no energy from it except that minute amount which impinges upon his organs of special sense. Thus it acts upon him not at all as a source of energy but entirely as a "signal." It might be said that what man does is to "scan" his social environment with his organs of special sense, which pick up "information" that is transmitted to his brain. His reaction to his social environment is therefore in proportion to the meaning of the "information" which he receives from it, rather than to the duration or magnitude of any of the events, situations, or other configurations which make up the signal. Thus it becomes apparent that the clinical observation that "man reacts to his social environment as he perceives it" cannot escape being correct, for the physical relationship between man and his social environment is such that he has nothing to react to except his perceptions.

This point is fundamental to understanding the implications of terms such as "the stress of modern living," "emotional stress," or "life stress." The term "stress" was brought into medicine from physics, where it is used to refer to a force within a solid body which is opposed to an external force, or "load." In physics, "load" and "stress" are proportional. In medicine, on the other hand, the internal response is seldom proportional to the external load, and, in the case of "life stress," it is almost never so. The changes which take place within the human as he relates to his social environment are derived entirely from his own energy stores and are set off entirely by his own regulatory mechanisms. The "stress," if this term may be used, is *sui generis;* the environment acts only as a signal.

The adaptation to the social environment is therefore mediated initially by the organs of special sense, which pick up information that is transmitted to the brain. The brain organizes all of man's reactions to his social environment and, in fact, makes possible the very society in which he exists. The brain presumably receives all of the mass of information supplied to it by the sense organs at any one time; but it selects those items

to which it will react.‡ However, the human brain generally reacts to the total life situation of its possessor at any given point in time, integrating the information which it receives into meaningful patterns and reacting to these patterns on the basis of information previously supplied to it, and that which was "built into it." Some of the information received by the brain enters "awareness" or "the conscious," and some does not, and reaction to the latter may be as vigorous as to the former.

There are many factors which determine how the brain will evaluate any one body of information which is brought to it. Among these is the "constitutional endowment" which includes much more than gross and fine structure; it includes such "built in" information as that which informs a newborn infant that a nipple placed in the mouth should be responded to by sucking; it includes the biological drives which shape a good deal of later behavior, and it includes all of those as yet undefined factors which are included in the term "constitutional temperament." In addition to this, there are the residual traces of the past information which has entered the brain, only part of which are available to conscious memory. This "learned endowment" of the person includes the knowledge, attitudes, beliefs, and behavior patterns which he shares with his society in general and the residual traces of the experiences peculiar to his own life. All of these, as well as the state of the man in general, and of his brain in particular, at the time the information is received are important determinants of its evaluation.

The function of the brain as an adaptive organ is not only that of integrating and evaluating the information which it receives from various sources, but also that of arriving at a solution which makes possible an adaptation to all of the requirements of human life. This operation, which is carried on largely outside of the realm of consciousness, must be extremely complex. Many of the adaptive reactions of the human organism—such, for example, as the adaptation to changes in CO_2 concentration in the blood, are organized at a cellular or organ level and can operate independently; but the more complex adaptations to the social environment, involving the actions of the organism as a whole, are organized and guided by the central nervous system. In order to facilitate the execution of such adaptive reactions, the brain is capable of enhancing, altering, diminishing, or even suspending, the functions of organs or cellular systems which might otherwise proceed automatically. The extent to which it is capable of influencing the entire internal economy is not generally appreciated, and it is probably for this reason, more than any other, that the effect of adaptive reactions upon human health is often underestimated. The brain has available to it as effector devices the "voluntary" nervous system, the "autonomic" nervous system, and the glands of internal secretion, and it appears to be capable of influencing any bodily process which is subject to the influence of any of these regulatory mechanisms. Furthermore, since the gross behavior of the organism is controlled by the central nervous system, all that may be affected by behavior, including total energy expenditure and the intake of foods, fluids, and potentially toxic substances, is ultimately under its influence also. Thus the potential capacity of the central nervous system for altering bodily processes is enormous.

Table 4 is a list of some of the indicators of bodily function which have been observed

‡ The basis for this selection is not entirely clear. Sometimes, as during sleep, the brain seems to disregard all but a minimum of the information which it receives. Likewise, when it is occupied with one body of information, it may refuse to consider additional information—as when a person is "preoccupied" with his thoughts, or has his "attention focused" upon something. The brain is capable of developing circular processes which, in their extreme forms as seen in the psychoses, cause it to refuse to consider almost any information, either internal or external, except that with which it is already dealing.

TABLE 4.—*Some Bodily Functions Which Have Been Observed to Change During Adaptations to Experimental Life Situations in the Laboratory*

Organ System	Function
Brain	Mood-thought-behavior, electrical activity of cortex, capacity to perform psychological tests, reaction to pain
General Metabolism	Oxygen consumption, CO_2 production, nitrogen excretion, blood glucose and ketone concentration, circulating eosinophiles, 17-hydroxycorticosteroid excretion
Circulatory	Cardiac rate, rhythm, electrical activity, ouput, stroke volume, exercise tolerance
	Blood pressure, peripheral resistance, arteriolar and capillary tone
	Pulsation and contractility of cerebral vessels
Blood	Relative viscosity, clotting time, erythrocyte sedimentation rate, prothrombin time, "sludging" phenomenon
Respiratory	Nasal secretion (amount and nature), redness, engorgement, edema; reaction to pollen, irritants, humidity, temperature
	Bronchial secretion, spasm
	Diaphragmatic movement
	Pulmonary ventilation
Gastrointestinal	Secretion of saliva
	Esophageal motility
	Gastric motility, redness and friability of mucosa, secretion of acid, pepsinogen, mucus, reaction to food, irritants, autonomic drugs
	Motility of duodenum and small bowel
	Motility, secretion, blood flow, pH, friability of mucosa, and lysozyme secretion of large bowel
Genitourinary	Renal blood flow, glomerular filtration rate, excretion of water, electrolytes, glucose, ketones
	Bladder motility
Bones and joints	Tonus of striated muscles
Skin	Temperature, reactive hyperemia threshold, itching, sebum secretion
Eye	Intraocular pressure, corneal vascularity, tearing

to be modified as human subjects adapt to experimental life situations in the laboratory.[3] These experimentally modifiable functions involve a majority of the organ systems and include processes of various types. The evidence from the laboratory suggests that there is no aspect of the human system which may not take part in, or be influenced by, adaptive reactions initiated by the brain in response to configurations of the social environment. All bodily processes may be so affected, and they may be enhanced, attenuated, stimulated, or depressed, to whatever degree each process is amenable to hormonal, nervous, or circulatory control, or subject to the influence of diet or activity. The effects of these alterations in body function may include increased vulnerability to tissue damage[4,5]; thus they may lead to the development of pathological processes which are irreversible and which may be permanently crippling, or even fatal.

Therefore, laboratory investigations and theoretical considerations, as well as clinical observations, provide good reason to believe that all "disease processes" may be to some extent influenced by the host's adaptation to his social environment. Some, being more labile, and involving bodily functions that are rapidly and markedly altered by nervous and hormonal influences, may respond rapidly and dramatically to the host's adaptations; others, less labile, and involving bodily functions that are more autonomous or slowly cumulative, respond less rapidly and dramatically, but perhaps in the long run to an equally great degree.

However, the nature of human adaptive reactions is such that some bodily processes are much more frequently disturbed by social adaptations than are others. In organizing adaptations to the social environment, the brain evidently utilizes all of the effector systems which are available to it, to whatever extent they are needed; but some adaptive reactions, like the suckling reflex of the baby, appear to be "written into it" and are used more often than others. They appear very early in life and are frequently evoked by a variety of stimuli thereafter.

An example is the nasorespiratory protective, associated with engorgement, redness, and hypersecretion of the nasal mucous membrane, blockage of airways, tearing, bronchospasm, and increased bronchial secretion. This reaction pattern is very frequently exhibited in the course of everyday life, being evoked by exposure to dust, smoke, fumes, cold air, and infectious agents, as well as by any situation which leads to crying. It has a direct adaptive value in each case, except in the case of crying. Here it may have an adaptive value of second order in that it may serve to give vent to emotion; but there is no possibility

that it will shut out or wash away the cause of the trouble, as it might in the case of noxious fumes. When exhibited under circumstances of grief, therefore, this reaction pattern has a degree of biological inappropriateness about it which is similar to that of the involuntary defecation that may accur with fear, or the finger-tapping of a tense man.

Some people, for reasons not entirely clear, exhibit this reaction pattern much more frequently and continuously than do most members of the population. It may well be that genetic factors are important in determining who will use this pattern excessively and inappropriately; but there is also good reason to believe that some people are conditioned by their life experiences so that they display this pattern when faced with various life situations which only in a symbolic sense require "shutting out and washing away." In any case, those who readily display this reaction make up a majority of those who have vasomotor rhinitis. They are hyperreactive to a variety of nasal stimuli, including infectious agents and allergens. Their chronic nasal engorgement and impaired drainage makes them more susceptible to sinusitis, and their capacity for developing bronchospasm and increased bronchial secretion renders them prone to bronchitis and asthma. Clinical observations have shown that all of these illnesses, each of which has several "causes," are more likely to appear when the host is facing a life situation which he perceives as difficult and to which part of his reaction is this nasorespiratory protective reaction.

This reaction pattern, and those involving the upper and lower gastrointestinal tract, the cardiovascular system, and the blood vessels of the head, are so exceedingly common that, along with the various symptoms of anxiety, tension, depression, and asthenia, they account for the majority of the symptomatic complaints experienced by the general population. This group of phenomena is often so easily associated with the patient's attitudes and emotions and so clearly "inappropriate" to the situations which evoke them that there has been a tendency to look upon them as a special category of illnesses, called "psychosomatic"; however, except for their lability, and the frequency of their appearance, there is no reason to believe that these reaction patterns, and the illnesses associated with them, are different from any other.

One would expect that a system, constructed as the human system is, would react to life experiences by manifesting various changes in its behavior, thought processes, mood, and bodily functions, and one would expect that these manifestations would usually take place simultaneously or consecutively, but that there would not necessarily be any fixed relationship between them. The findings from our investigation support this hypothesis. The occurrence of illnesses in "clusters," with each "cluster" occurring during a period of adaptive effort and consisting of a variety of illnesses involving several body systems and appearing consecutively or concurrently, is what one would expect if this hypothesis were correct. The great majority of the illnesses which make up these clusters involve micro-organisms, toxic material, physical traumata, dietary disturbances, and other recognizable causative agents. In many cases the form which a disease takes is in part dictated by this "causative agent" and there is much reason to believe that the illness could not appear in just this form in its absence. Even where the illness appears to be simply the result of the excessive or prolonged use of a "biologically inappropriate reaction pattern" it may well be that the propensity of the person to react in this manner has a genetic or constitutional basis. However, the evidence from these studies also indicates that although man is surrounded throughout his life by a host of potential "causative agents" of disease and carries with him always his genetic susceptibilities, he develops illness most frequently at times when he is having difficulty adapting to his environment. It appears that the disturbances of bodily

function, mood, thought, and behavior which occur during periods of adaptive effort make possible the appearance of disease processes which might not otherwise manifest themselves. It is our general inference that man's relation to his social environment has relatively small influence upon the form which illnesses will take but that it has a major influence upon the time and the situation in which illnesses will occur and the course which they will pursue.

Conclusions

1. Members of the otherwise homogeneous adult populations exhibit differences in their general susceptibility to illness such that some persons experience a greater number of illnesses per unit time than do others.

2. Those persons exhibiting the greater susceptibility to illness exhibit a greater susceptibility to all forms of illness such that the greater the number of episodes of illness which they experience the greater the number of organ systems which are likely to be involved. Those having the greater number of bodily illnesses are likely to experience more accidents and more disturbances of mood, thought, and behavior.

3. In general, illnesses are not distributed at random over the life of a person but often appear in "clusters." A cluster is usually of several years' duration and includes a number of illnesses of various etiologies involving a number of organ systems and appearing concurrently or consecutively. Such clusters alternate with periods of relatively good health which are of variable duration.

4. Clusters of illness most often appear when a person is having difficulty adapting to his environment as perceived by him. Those persons who exhibit a high susceptibility to illness are those who exhibit the greatest difficulty in adapting to their life situations.

5. Differences in the amount of illness exhibited by different men appear to be in part the result of inherent differences in their adaptive capacities and in part the result of differences in the environmental situations which they encounter.

6. Man's relation to his social environment appears to have small influence upon the form which illnesses will take but a major influence upon the time and the situation in which illnesses will occur and the course which they will pursue.

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ABSTRACT OF DISCUSSION

DAVID E. ROGERS, New York: Dr. Hinkle has presented some extremely interesting material derived from study of three relatively homogenous groups of people. His data suggest that human reactions to environmental stresses and strains may determine, in part, the frequency with which they become ill.

Certain findings in the present study seem of particular interest to me. Dr. Hinkle has shown a positive correlation between the total number of illnesses sustained by each person and the number of organ systems involved. This is not what one would expect if specific structural defects in one organ system were responsible for frequent and recurrent illness. He has also shown a positive correlation between the total number of major and minor illnesses sustained by the same person and has indicated that people with many illness episodes have more accidents. These data indeed suggest that susceptibility to illness may be related to broad changes in the human host rather than local organ susceptibility.

Other studies lend weight to Dr. Hinkle's hypothesis that reaction to stress perceived, but not directly experienced, may heighten susceptibility to illness.

For example, it has been shown that a wide variety of nonspecific stimuli which alter the respiratory tract mucosa of mice can lead to activation of a latent viral pneumonitis in these animals. Activation of the infection apparently results from the local mucosal change, regardless of how it is produced. Dr. Harold Wolff and his associates have clearly demonstrated that human reactions to stimuli of a perceptual rather than physical or chemical nature can produce definite, measurable alterations in mucosal structure and function. These mucosal changes mimic those seen following direct chemical or allergenic insults. It thus seems reasonable to believe that changes in the host which result from his reactions to his environment may predispose to increased episodes of illness.

I am inclined, however, to differ with Dr. Hinkle in certain of his conclusions. I am reluctant to assign any causal relationship to the finding that the majority of patients having a large number of ill-

ness episodes have more severe psychosocial conflicts. In the body of his paper Dr. Hinkle indicates that a positive correlation exists between these two phenomena without attempting interpretation. In his discussion he assumes a causality which I do not believe is justified from the material he reports.

I am not convinced that the data presented demonstrate a clear relationship between disorders of mood, thought, and behavior (subjective data) and the number of total illnesses (objective data) sustained by the persons studied. Further, the evidence presented to substantiate this correlation is derived from studies on the Chinese group, where actual records of previous illness were lacking. Data obtained from personal recall alone introduces an individual memory bias and distortion which cannot be properly evaluated.

Such retrospective data can be misleading. The wide discrepancies in the reported incidence of congenital anomalies following maternal rubella furnish a striking example of the difficulties involved in judging the accuracy of recalled information. Original studies, in which mothers recently delivering babies were interviewed, indicated that an 80% chance of fetal congenital anomalies existed when maternal rubella occurred during the first trimester of pregnancy. Subsequent prospective studies, in which expectant mothers contracting rubella during the first three months of pregnancy were followed to term, have indicated an actual incidence of congenital anomalies of less than 20%. In reviewing these studies it appears clear that mothers who delivered abnormal children could recall episodes of German measles occurring during pregnancy while those who had healthy infants could not.

I feel this aspect of the present study will be strengthened if testing procedures, which give us more understanding of the patient's inner concept of self and his life situation, substantiate the present hypotheses. I am certain, as is Dr. Hinkle, that the way socioenvironmental problems are perceived by the person who is experiencing them has considerably greater meaning than our external evaluation of their significance. In the present study it is of interest that in certain of the persons studied a striking negative correlation existed between the life situations as externally evaluated and amount of illness experienced.

I think this finding may indicate, in part, how difficult it is to assess accurately, as outside observers, the true meaning and flavor of life situations to the persons who are living them.

Testing procedures such as the Q-sort technique, projective questionaires, and the Thematic Apperception Test, which allow patient expression of attitudes toward self and surrounding, might further define the type of personality setting and situation in which illness ensues. Such data would require less external interpretation by the investigators and might furnish more valid correlations with objectively recorded illness.

Dr. Hinkle has indicated that such studies have been carried out on some patients. I am thus anxious to learn whether any correlations can yet be made between findings derived from such inner reference testing procedures and the incidence of illness in these groups.

I think Dr. Hinkle is to be congratulated in objectively exploring an area of vast importance to all of us concerned with human illness. To date, the investigative tools which can be focused on the complex problem of man's relationship to his abstract environment are relatively crude. Nevertheless, during recent years Dr. Hinkle and Dr. Wolff have reported an increasing number of controlled observations on the changes in the human organism which can result from perceptual stimuli. This type of approach has already yielded considerable data which can be checked, retested, and subjected to critical evaluation by other investigators.

In all other medical disciplines, the scientific method has rapidly increased our ability to understand and deal with disease. More precise and verifiable knowledge about the type of life setting in which illness is likely to arise studied in this manner may allow us to deal more effectively with the problem of the frequently "sick" person in the future.

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Acute Erythroblastopenia

Pathogenesis, Manifestations, and Management

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The hemolytic crises observed in patients with familial spherocytosis were initially thought always to represent a rapid increase in magnitude of the existing hemolytic process. It was first recognized by Lyngar [1] that, in some of these cases at least, the crisis was due to a sudden decrease in red cell delivery rather than to an increase in the rate of hemolysis. However, the significance of his observations was overlooked until Owren [2] reported a series of six crises, four of which occurred sequentially in members of a family with familial spherocytosis. In all of these patients severe anemia, thrombocytopenia, and reticulocytopenia were noted. The most significant observation, however, was bone marrow hypoplasia during the crisis, predominantly involving the erythroid elements. The myeloid and megakaryocytic elements showed only slight left shift, although granulocytopenia and thrombocytopenia were present at the time. This observation, plus the demonstration of a simultaneous decrease in reticulocytes, serum bilirubin, and urine urobilinogen, led Owren to reject the idea that these crises were due to an increase in the rate of hemolysis. Instead, he proposed that the rate of the hemolytic process continued unaltered, while the erythroid hypoplasia sufficiently interferred with erythrocyte delivery to permit the development of the rapidly progressive anemia. Owren's postulations as to the pathogenesis of these crises have subsequently proved to be true in some instances, although it seems that there are also occasions in which a rapid increase in the rate of hemolysis may occur.[3]

Subsequent to Owren's observations, similar "aplastic crises" have been described in other types of hemolytic disease. Singer et al.[4] first described such a crisis in a patient with sickle-cell anemia, and Chernoff [5] later reported four additional cases. There are two reports in the literature of an aplastic crisis complicating an acquired hemolytic anemia,[6,7] two associated with paroxysmal nocturnal hemoglobinuria,[8,9] and one in an infant with erythroblastosis fetalis.[7] In addition to these, all of which occurred during the course of well-proved hemolytic states, Gasser [10] has convincingly demonstrated the occurrence of erythroid hypoplasia, or acute erythroblastopenia, during the course of infectious diseases, anaphylactoid purpuras on an allergic basis, and various drug hypersensitivities. These all occurred in patients with no other demonstrable hematologic abnormality or hemolytic process. Chernoff [5] likewise reported one case occurring in a child during the course of infectious mononucleosis. The latter examples suggest that acute erythroblastopenia may occur during the course of acute stress-provoking situations but in the absence of hemolysis results in such a mild anemia that it goes unnoticed.

The purpose of this report is to describe two additional cases of acute erythroblastopenic crises and to discuss the pathogenetic and therapeutic implications.

Report of Cases

CASE 1.—A 24-year-old married white woman was first admitted to the John Sealy Hospital on Sept. 20, 1950, with a history of having had "the

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yellow jaundice ever since I was born." The patient's menarche did not occur until the age of 17. A physician told her that this was due to the fact that her "blood was low." No other siblings or members of her family were similarly affected.

Physical findings revealed pallor and hepatosplenomegaly. Laboratory studies at that time showed a normochromic normocytic anemia, reticulocytosis, and slightly low platelet count. This anemia was proved to be hemolytic in nature by the demonstration of a fecal urobilinogen of 1100 mg/100 gm. of stool. A direct Coombs test was negative. A bone marrow examination revealed intense normoblastic erythroid hyperplasia. Osmotic fragility studies were normal. Hematologic studies on other members of her immediate family were within normal limits. On the basis of the above studies the patient was thought to have an acquired hemolytic anemia of unknown etiology.

On Oct. 9, 1950, a splenectomy was performed. Pathologically the spleen revealed only "congestion," while a lymph node biopsy showed "hyperplasia."

The definite hematologic benefit she received following splenectomy was short-lived, however, for following the uncomplicated birth of her first child on Dec. 1, 1950, the severity of the hemolytic process seemed to increase, as evidenced by a gradual fall in hemoglobin levels and an increase in reticulocytosis.

On Aug. 10, 1951, the patient was readmitted for further study. A marrow examination again revealed normoblastic erythroid hyperplasia, while liver biopsy showed "minimal portal cirrhosis and extramedullary hematopoiesis." Treatment with intravenous corticotropin (ACTH) did not decrease the severity of the hemolytic process, and she was discharged unimproved.

On Oct. 21, 1952, she was again admitted, and additional studies at this time revealed, as before, a hemolytic anemia of unknown cause. On Nov. 17, 1952, the patient extruded a 45-day-old fetus, although she had not known that she was pregnant. On. Dec. 2, 1952, an exploratory laporatomy was performed to search for accessory spleens, but none were found.

During 1953 she was followed on an outpatient basis and continued to hemolyze briskly, necessitating frequent transfusions of packed red cells. Treatment with oral cortisone during this time effected no substantial benefit.

On March 25, 1954, the patient, who was again pregnant, was admitted in labor and delivered of a normal infant without difficulty.

For the next year she did relatively well clinically, though still hemolyzing at a rapid pace. On March 23, 1955, she came to the emergency room with an oral temperature of 104 F. Examination revealed severely inflamed tonsils. She was given penicillin and seen the next day at the medicine clinic, at which time her temperature was still 104 F. A peripheral blood cell count at that time revealed a hemoglobin of 8.3 gm/100 cc. and a leukocyte count of 11,000/cubic millimeter. On March 29, 1955, she was seen in the hematology clinic, where she was found to be critically ill. The hemoglobin at that time was only 4.8 gm/100 cc., and only occasional reticulocytes were seen in the peripheral blood. At this point an acute erythroblastopenic crisis was suspected, and she was admitted. A bone marrow examination at this time revealed a distinct decrease in erythroid activity in contrast to previous studies. Of the few erythroid elements seen, the majority were early erythroblasts. An erythrocyte survival half-time (T-½), as measured by the radioactive chromium technique, was found to be six and one-half days (our normal range, 50-65 days). This is roughly equivalent to about 13 days as measured by the Ashby technique.

Oral hydrocortisone and intramuscular repository corticotropin injection were begun immediately, and during the next 24 hours three units of packed red cells were administered. A bone marrow biopsy on April 1, 1955, three days after admission, showed a tremendous increase in the number of erythroid elements. There were still almost no mature cells of the erythroid series, and the predominant cell was the early erythroblast. Another marrow specimen, on April 4, 1955, showed a marked shift to the right in the maturity of the erythroid series, and the picture was that of normoblastic hyperplasia.

As the marrow cellularity increased, the patient began to experience excruciating bone pains involving principally the long bones and the vertebrae. Since this correlated so well with the striking increase in marrow cellularity, it was postulated that the bone pain probably was due to the rapid expansion within the rigid confines of the marrow cavity. By the fifth hospital day her reticulocyte count had risen to 2.8%, and it continued to rise steadily thereafter to higher levels. She continued to do well clinically and was discharged in a relatively stable hematologic state with, however, evidence of continuing hemolysis. She was maintained on repository corticotropin injection intramuscularly and oral hydrocortisone for several weeks after dismissal, and they were then discontinued. Subsequently the hemolytic process again increased in intensity, and the administration of corticotropin and hydrocortisone was reinstituted. She has been maintained on them continuously since that time.

Case 2.—A 25-year-old Negro man was seen for the first time in John Sealy Hospital on May 16, 1955, in the emergency room, with the chief complaint of pain in the abdomen. The present

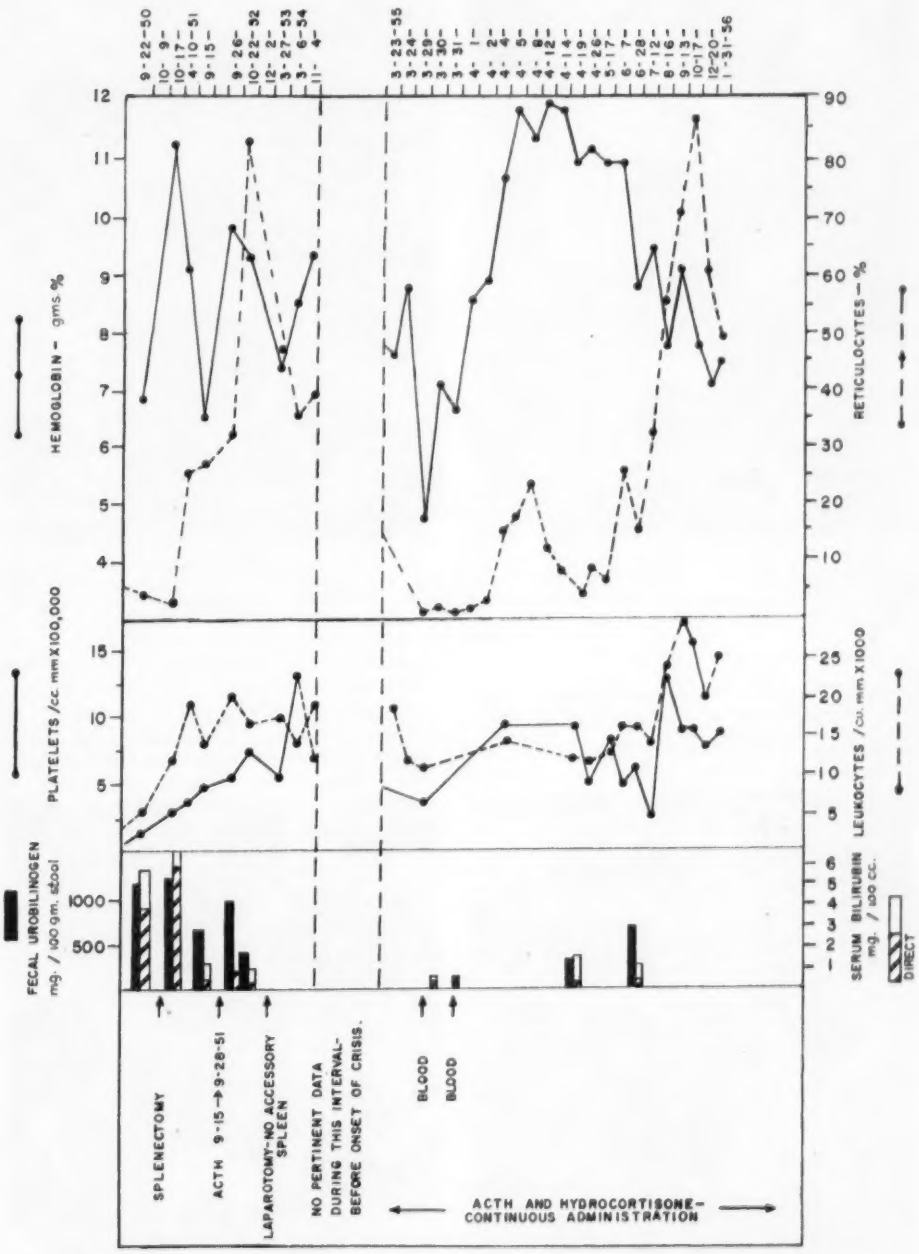


Fig. 1. (Case 1).—Graphic representation of the clinical course of the patient with acquired hemolytic anemia during the five years she has been followed. The acute erythroblastopenic crisis with the drastic fall in hemoglobin, and fecal urobilinogen is apparent. Only the blood transfusions administered during the crisis are shown on this graph.

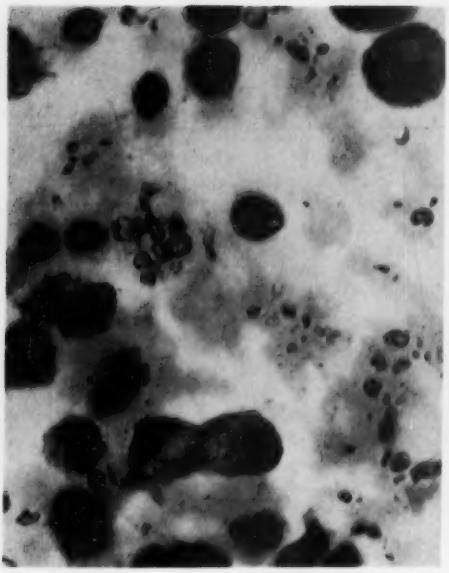


Fig. 2 (Case 1).—Bone marrow on March 29, 1955, showing definite erythroid hypoplasia at the height of the crisis. Only granulocytes and lymphocytes are seen; reduced from mag. × 900.

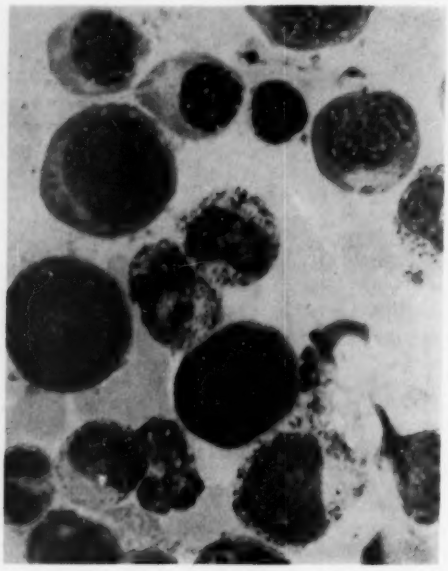


Fig. 3 (Case 1).—Bone marrow on March 31, 1955 showing beginning erythroid regeneration with large numbers of megaloblasts and early erythroblasts; reduced from mag. × 900.

Fig. 4 (Case 1).—Bone marrow on April 4, 1955, showing impressive erythroid hyperplasia. Maturation has progressed, and now there is a preponderance of late erythroblasts and normoblasts; reduced from mag. × 900.

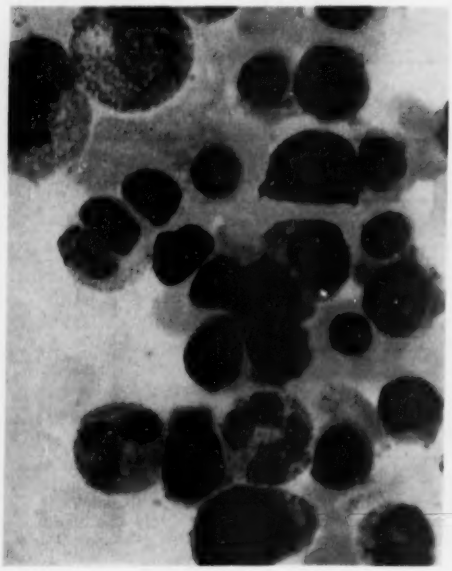
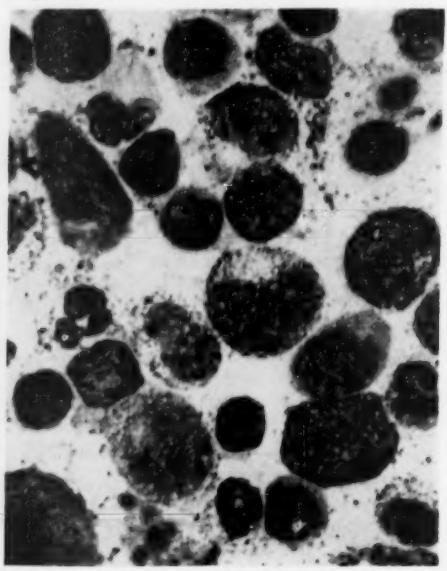


Fig. 5 (Case 1).—Bone Marrow on April 14, 1955, reveals a return to the precrisis picture of normoblastic erythroid hyperplasia; reduced from mag. × 900.



illness had begun suddenly the night previously, when he had experienced a shaking chill followed by fever and the gradual development of colicky pain in the right lower quadrant, radiating down the anterior aspect of the right thigh. Nausea developed, and the patient vomited twice. Mild dysuria had also been present. He had had a "cold" for three or four days before the onset of the present illness. Past history revealed that he had always been in good health (although his mother subsequently stated that he had been "anemic" in the past).

On physical examination, the patient was found to be acutely ill, with oral temperature of 103 F. There was pallor of the mucous membranes, the sclerae were icteric, and a blowing systolic murmur was heard at all valve areas. There was generalized tenderness over the abdomen, most marked in the right lower quadrant, with muscle-guarding in this area and tenderness on the right on rectal examination. No bowel sounds were heard on auscultation of the abdomen. The hemoglobin level at this time was reported at 7.8 gm/100 cc., and the leukocyte count, 15,000/cubic millimeter, with a shift to the left. The reticulocyte count was 11%, and 4 normoblasts/100 leukocytes were noted. A rapid test for sickling (sodium metabisulfite) revealed 59% sickling in one-half hour. It was felt by both medical and surgical consultants that the patient had a hemoglobinopathy (either hemoglobin S-C disease or atypical sickle-cell anemia), but in view of the classical physical findings of acute appendicitis, an exploratory laparotomy was imperative. The findings at surgery were those of a mesenteric adenitis. The appendix, which was removed, was considered to be normal, although there was obliteration of the lumen.

The next morning, in spite of minimal blood loss at surgery, the hemoglobin level had fallen 2 gm/100 cc., the reticulocyte count had dropped to 2.2%, and a bone marrow examination the following day (May 18, 1955) showed nearly complete absence of erythroid elements, with only an occasional erythroid cell seen on the entire specimen. The myeloid cells were decreased in number and showed severe toxic changes; the megakaryocytes appeared decreased in number. At this point it was recognized that the patient was experiencing an acute erythroblastopenia. By the following day in spite of a transfusion of 500 cc. of whole blood, the hemoglobin level had dropped to 4.9 mg/100 cc.; no reticulocytes were present in the peripheral blood. Treatment consisted of repository corticotropin injection intramuscularly and oral adrenocortical steroids, aqueous penicillin, and streptomycin for a postoperative bilateral bronchopneumonia, and transfusions of packed erythrocytes as needed (a total of 7 units during the hospitalization). Bone marrow examination on the fourth day of the crisis showed a marked increase in cellularity, with the most striking increase being in the erythroid elements. Most of the cells in the erythroid series were megaloblasts or early erythroblasts. Serial bone marrow examinations showed further increase in cellularity, with a progression of maturity of the erythroid elements. By the 10th day of the crisis reticulocytes in the peripheral blood numbered 2.6% and steadily rose thereafter.

The hemoglobin of blood obtained before surgery or transfusion was subjected to paper electrophoresis; only S type hemoglobin was demonstrated. With this confirmation, it was felt that the diagnosis of sickle-cell anemia was firmly established. Our final impressions in this case were that a sickle-cell crisis was likely responsible for the abdominal pain and that the appendectomy in all probability precipitated the acute erythroblastopenic crisis.

Comment

In view of the fact that acute erythroblastopenia is being recognized with increasing frequency in an expanding spectrum of disease processes, it is appropriate to discuss the problem from the following standpoints: I. Antecedent Diseases; II. Etiologic and Predisposing Factors; III. Aspects of Erythrocyte Formation and Production of the Crisis; IV. Clinical Picture; V. Diagnostic Criteria and Laboratory Studies, and VI. Clinical Course and Management.

I. Antecedent Diseases.—Erythroblastopenic, or aplastic, crises may occur either in patients with an established hemolytic process or hematologically normal persons as a complication of a variety of acute processes. A listing of the cases of aplastic crises reported in the literature is to be found in the accompanying Table.

II. Etiologic and Predisposing Factors.—A. Hypersplenic Effect and Maturation Arrest Versus Erythroid Hyperplasia: In 1948 Dameshek and Bloom [15] noted that the bone marrow examinations in seven cases of familial spherocytosis with crises were markedly hyperplastic, with an increase in early erythroid elements but a paucity of more mature forms. As a consequence it was suggested that the crises in these patients were due to (1) a maturation arrest

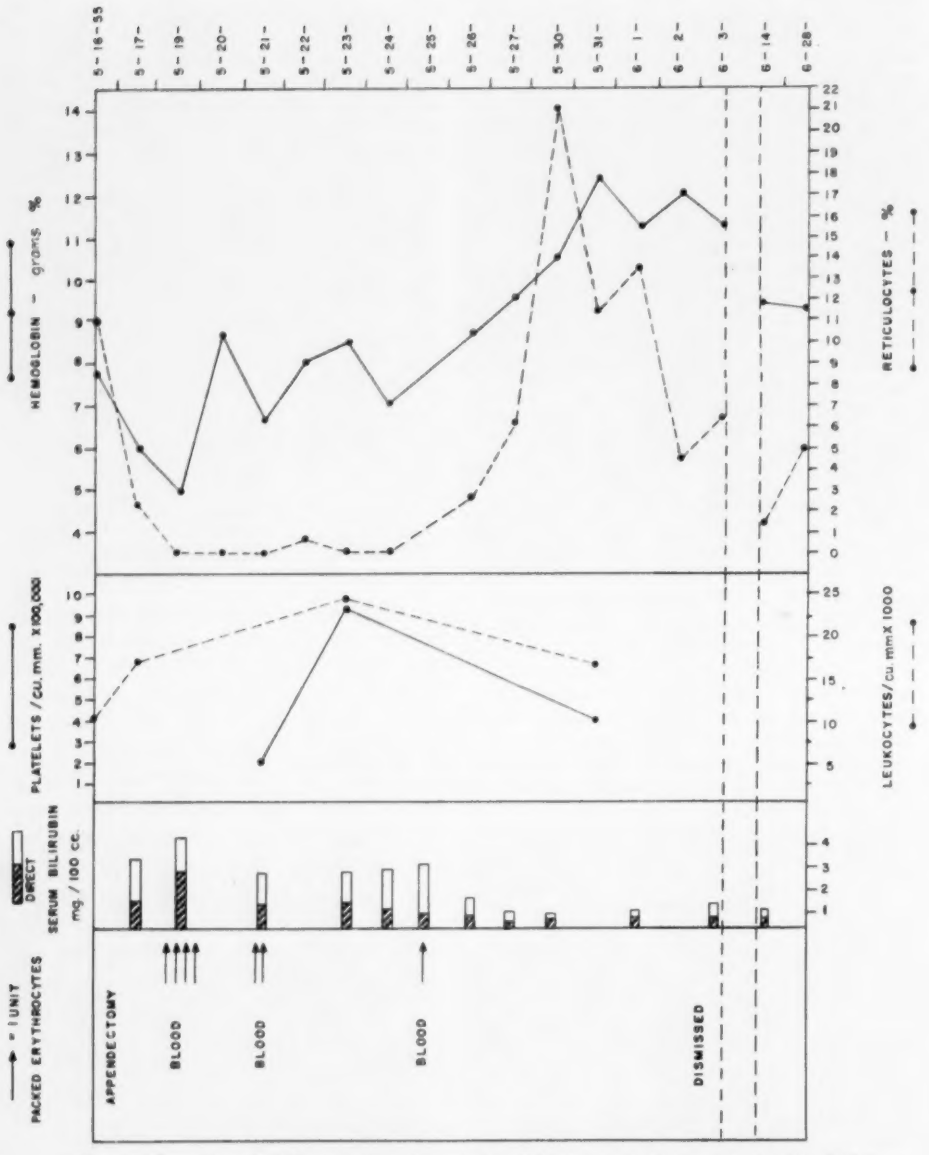


Fig. 6 (Case 2).—Graphic representation of the clinical course of the patient with sickle-cell anemia. Note the development of the erythroblastopenic crisis following the appendectomy.

of erythroid elements in the bone marrow and/or (2) an exaggeration of the already existent hemolytic mechanism. It was further postulated that a "hypersplenic" factor might be causal in the production of maturation arrest and that splenectomy might be beneficial. However, during the past few years increasing numbers of cases have been carefully studied, and it now seems probable that the marrow samples were obtained from these patients during the regenerative phase of the crises. If the marrow had been examined earlier, hypoplasia of the erythroid series would likely have been seen. While

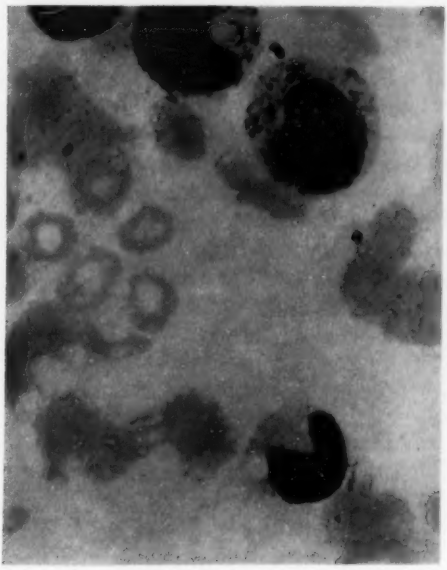


Fig. 7 (Case 2.)—Bone marrow on May 18, 1955, revealing an almost total absence of erythroid elements; reduced from mag. × 900.

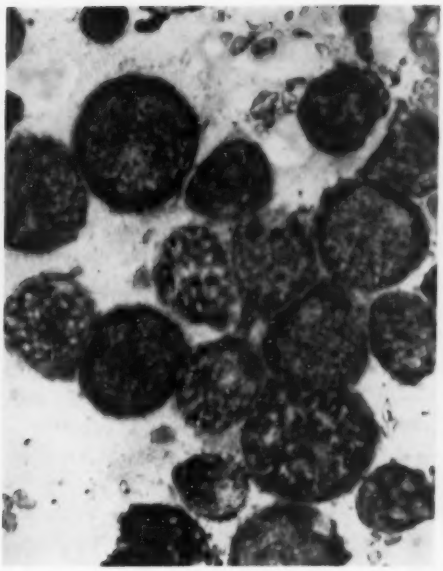


Fig. 8 (Case 2).—Bone marrow on May 23, 1955, showing a marked increase in erythroid proliferation chiefly at the early erythroblastic level; note mitotic figures; reduced from mag. × 900.

Fig. 9 (Case 2).—Bone marrow on May 25, 1955, showing an increase in maturity of erythroid elements which are chiefly late erythroblasts; reduced from mag. × 900.

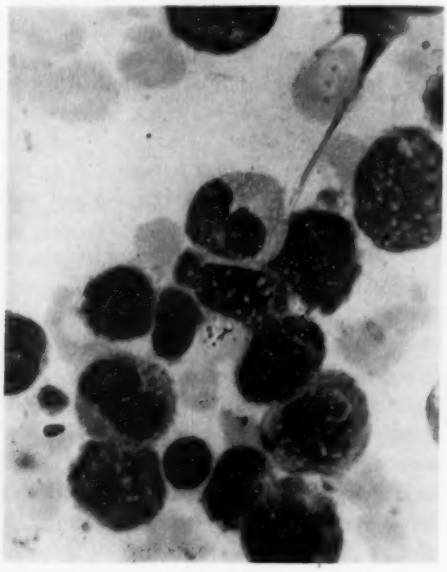
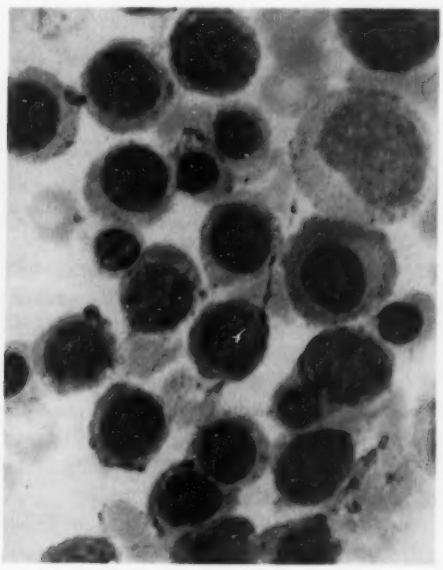


Fig. 10. (Case 2).—Bone marrow on June 14, 1955, showing an almost complete return of the stimulated erythroid elements to a normoblastic and late erythroblastic level of maturation; reduced from mag. × 900.



Erythroblastopenic Crises Reported in the Literature

Diseases	Authors	No. of Cases
Antecedent hemolytic disease		
1. Familial spherocytosis	Scott[11]	4
	Murray-Lyon[13]	2
	Dedichen[13]	13
	Lyngar[1]	3
	Horne et al.[14]	6
	Owren[8]	7
	Dameshek et al.[12]	7
	Li et al.[16]	5
	Marson et al.[17]	3
	Battle[18]	3
	Ingham[19]	5
	Margolis[20]	3
	Gasser[10]	1
	Haase[21]	2
	Total	64
2. Sickle-cell anemia	Chernoff et al.[5]	4
	Singer et al.[4]	1
	Total	5
3. Acquired hemolytic anemia	Davis et al.[6]	1
	Gasser[10]	1
	Total	2
4. Erythroblastosis fetalis	Gasser[7]	1
5. Paroxysmal nocturnal hemoglobinuria	Crosby[9]	1
	Larrain et al.[9]	1
	Total	2
No antecedent hematologic disorder		
1. Allergies		
(a) Anaphylactoid purpura	Gasser[10]	3
(b) Drug idiosyncrasies	Gasser[10]	2
	Total	5
2. Infections		
(a) Primary atypical pneumonia	Gasser[10]	1
(b) Diphtheria	Gasser[10]	1
	Total	2
3. Miscellaneous		
(a) Infectious mononucleosis	Chernoff et al.[5]	1
(b) Subsepsis allergica	Kölbl[22]	1
	Total	2

maturation arrest of the erythroid series probably does not exist during such a crisis, it is difficult to generalize in regard to myeloid and megakaryocytic cells. Usually neither of these marrow elements is depressed, and they show only a left shift. It is possible that there might be some degree of maturation arrest of these elements in those patients with erythroid hypoplasia who demonstrate peripheral leukopenia and thrombocytopenia with no concomitant depression of their marrow precursors.

B. Preceding Infections: That infectious processes can trigger the onset of acute erythroblastopenic crises seems well established in a number of cases. Singer's case of a child with sickle-cell anemia[4] seemed definitely related to an antecedent pneumonitis which was subsequently diagnosed as primary atypical pneumonia on the basis of a rising cold agglutinin titer. Gasser[10] has reported a case following an episode of primary atypical pneumonia, another during the course of a case of diphtheria, and another following scarlet fever. Chernoff[5] reported definite erythroblastopenia in the bone marrow of a child with infectious mononucleosis, although only a very mild anemia developed subsequently. A septicemia due to Salmonella choleraesuis precipitated the crisis in one of the children with sickle-cell anemia reported by Chernoff.[5]

In addition to these cases in which infectious agents were definitely implicated, there are a larger number of instances wherein the crises have been preceded for a week or more by a vague illness, most often suggestive of a respiratory infection or influenza.

Actually, one of the most striking features has been the serial occurrence of the crises in closely associated members of families with familial spherocytosis. In 1935, Scott[11] reported the onset of crises in a time-related sequence in four patients with familial spherocytosis. Dedichen[13] reported crises in 13 members of two neighboring families in Norway. In 1945, Horne[14] reported crises in a mother and four children of a family of eight. In the latter two series there was a definite time relationship, and each of the crises developed within a few days of one another.

Because of the above instances of wholesale "epidemics" of aplastic crises, some extrinsic infectious agent was reasonably suspected to be a precipitating cause of the episodes. Dedichen[13] suggested that a contagious respiratory infection was responsible for the initiation of the crises. Horne[14] suspected influenza to be the culprit (there had been a recent epidemic) and placed a ferret, an animal highly susceptible to infection by the influenza virus, in the home of

one of the families. The animal died later, suggesting that the influenza virus might have been responsible for precipitating the crises. Other similar instances of a preceding upper respiratory infection are too numerous to mention individually. In both of our cases the erythroblastopenic crises were preceded by upper respiratory infections. It seems logical, therefore, to suggest that a preceding viral infection may often precipitate aplastic crises in susceptible persons, although specific proof is lacking.

C. Allergic States: An interesting series of observations was reported by Gasser,[10] who noted the development of transient erythroblastopenia in the marrows of children following a variety of allergic reactions. In one of these cases, a child bitten by a mosquito later developed anaphylactoid purpura and a transient erythroblastopenia and eosinophilia of the marrow. There were two other examples of patients with anaphylactoid purpura of uncertain etiology who developed erythroblastopenia. Kölbl[22] has reported a case of erythroblastopenia on the basis of subsepsis allergica (septic temperature, transitory swelling of the joints, and repeated appearance of urticaria, "rheumatoid" heart, and palpable spleen). During the episode a positive direct Coombs test was demonstrated.

Gasser has likewise reported several instances of drug idiosyncrasies followed by erythroblastopenia.[10] One patient who had received phenobarbital sodium developed an eruption and fever followed by erythroblastopenia, while another developed erythroblastopenia following a course of chenopodium oil (for intestinal ascariasis).

All of these cases reported by Gasser were clinically mild, with only minimal changes noted in the peripheral blood. In view of these and other observations, it seems likely that erythroblastopenia following allergic reactions and drug hypersensitivities occurs far more commonly than is presently recognized.

D. Trauma: The role of physical trauma in the causation of aplastic crises has not been mentioned often. Therefore, it is pertinent to call attention to one patient with familial spherocytosis reported by Gasser[10] in whom an erythroblastopenic crisis followed the performance of a tonsillectomy. It is also very probable that in the patient with sickle-cell anemia described herein (Case 2) the crisis was precipitated by an appendectomy.

III. Dynamics of Erythrocyte Formation and Production of the Crisis.—In the discussion of erythrocyte production the initial consideration is the dynamic nature of erythropoiesis. At any one time the number of erythrocytes in the peripheral blood represents the result of a dynamic equilibrium which has been established between the formation of erythrocytes and the removal of effete erythrocytes by the spleen and reticuloendothelial system. In a normal human, erythrocytes have a survial time of approximately 120 days, as determined by the Ashby differential agglutination technique, or an erythrocyte survival half-time (T-½) of 50 to 65 days as determined by the radioactive chromium technique. The bone marrow replenishes the destroyed erythrocytes at an equivalent rate. However, certain disease states are associated with an increase in the rate of destruction of erythrocytes, evidenced by a shortened survival time, due to (1) defects in the formation of the erythrocytes (as in familial spherocytosis and thalassemia), (2) the presence of abnormal hemoglobins (such as hemoglobins S, C, D, E, etc.), or (3) sensitization of the red cells by antibodies.

As the rate of erythrocyte destruction increases, the bone marrow output of erythrocytes likewise increases. As long as it is able to keep pace with the rate of destruction, the number of erythrocytes in the peripheral blood will remain constant, and the hemolytic process is said to be in a "compensated" state. The ability of the bone marrow to increase its output is considerable. Crosby and Ackeroyd[23] have calculated that under extreme degrees of stimulation the functionally normal marrow

is capable of increasing its output sixfold (which could theoretically compensate for a survival time of as low as 20 days). When the demand exceeds the capacity of the marrow to respond, anemia develops and the hemolytic process is in a "decompensated" state. This "decompensated" state may be the result of (1) such a severe hemolytic process that even a marrow capable of responding to maximal stimulation cannot keep pace or (2) inability of the marrow to realize its potential capacity due to functional impairment. This inability of the marrow to respond maximally has been termed "dyserythropoiesis."[24]

It is apparent, therefore, that an anemia will develop either if the rate of hemolysis increases inordinately or if red cell delivery is retarded. In acute erythroblastopenic crises there is an abrupt and almost complete cessation of erythropoiesis. This disruption is usually self-limited and lasts from 7 to 10 days. In a hematologically normal patient whose cells have a survival time of 120 days, 10 days of erythroid aplasia will not be sufficient to produce a profound change in the peripheral blood. This latter observation is exemplified by the patient with infectious mononucleosis reported by Chernoff,[5] who demonstrated a drop in hemoglobin from 12.1 to 9.8 gm/100 cc. and a drop in erythrocytes from 4,000,000 to 3,200,000/cubic millimeter in 13 days. Similar examples were noted in some of Gasser's cases.[10] It follows, therefore, that a high index of suspicion is necessary if erythroblastopenia in patients without hemolytic disease is to be demonstrated.

Conversely, it is clear that when a hemolytic disease is complicated by retardation of erythropoiesis, the situation is much more serious. Inasmuch as the survival time may be as short as 15 days in severe hemolytic states, any interference with erythrocyte delivery will produce a precipitous drop in hemoglobin and erythrocyte values. If erythroid hypoplasia lasts 10 days, there may be a fatal outcome if adequate treatment is not instituted. In the patient with acquired hemolytic anemia (Case 1), the survival time was found to be only 13 days (erythrocyte survival half-time [T-½] of 6½ days). Her hemoglobin level fell from 8.3 to 4.8 gm/100 cc., and the erythrocytes, from 2,300,000 to 1,380,000 cubic millimeter in five days. These figures indicate how rapidly a critical anemia may develop when reduction of erythrocyte survival time and erythroid hypoplasia coexist.

Singer[4] prefers to call this phenomenon "delivery crisis," rather than "aplastic crisis," since disturbances in delivery of erythrocytes may possibly be due to other factors. He emphasizes the work by Reinhard et al.[25] and Tinsley et al.[26] in which suppression of erythropoiesis and moderate erythroid hypoplasia in patients with sickle-cell anemia and familial spherocytosis was produced by administration of high concentrations of oxygen. Since erythrocyte destruction continued, these patients experienced appreciable drops in erythrocyte and hemoglobin values. In light of the above information, "delivery crisis" might seem the preferable appelation for this process, although it is not in common use.

IV. Clinical Picture. — No diagnostic clinical picture is seen during an erythroblastopenic crisis. The patients commonly experience malaise, fever, and headaches. Symptoms and signs resulting from the rapidly progressing anemia usually develop. Retinal hemorrhages may occur. One clinical observation which was impressive in the patient with acquired hemolytic anemia was the development of severe bone pain involving chiefly the long bones and vertebrae. At the same time that this bone pain developed, a tremendous increase in marrow cellularity was demonstrated due to beginning erythroid regeneration. It seems likely that the bone pain resulted from the rapid increase in marrow volume occurring within the bony unyielding marrow cavity. Measurement of intramedullary pressure would have been valuable in the confirmation of this suggestion.

V. Diagnostic Criteria and Laboratory Studies.—The occurrence of an increasingly severe anemia and reduction or complete absence of reticulocytes in the peripheral blood, particularly in a patient with a preexisting hemolytic process, should immediately suggest the possibility of erythroblastopenic or aplastic crisis. As indicated previously, in patients with no antecedent hemolysis, the resulting anemia is much milder and more insidious in its onset and may escape detection.

Once an erythroblastopenic crisis is suspected on the basis of the above observations, a bone marrow examination must be performed immediately in order to prove the diagnosis. If such a crisis exists there is an impressive erythroid hypoplasia with an almost total absence of erythroid elements. A few observers have reported the presence of peculiar giant cells in the marrow of patients during erythroblastopenic crises.[10,22] These cells are approximately 60μ in diameter, with extremely large nuclei measuring 25μ to 35μ. The chromatin is finely divided and loose in structure and resembles that of early erythroid cells. For this reason it is thought that these giant cells probably represent abnormal erythroid precursors. The bone marrow also often shows an increase in reticulum and plasma cells.

In addition to the anemia and reticulocytopenia in the peripheral blood, leukopenia and/or thrombocytopenia may also be seen, though this is not a constant observation by any means. The cause of the leukopenia and thrombocytopenia is not so easily determined. Myeloid elements in the marrow may be relatively normal in appearance or show only moderate left shift and qualitative changes. Some observers have noted the presence of giant neutrophils in the bone marrow.[10] Megakaryocytes are usually normal both quantitatively and qualitatively. The origin of the leukopenia and thrombocytopenia remains obscure, although there is a possibility that they reflect an interference with maturation of these elements.

During the erythroblastopenic crisis the indirect serum bilirubin, which may already be elevated because of preexisting hemolysis, remains constant or may even fall. This, together with the observation that the level of fecal urobilinogen excretion is either decreased or unchanged (Case 1), clearly demonstrates the fact that there is usually no increase in the rate of hemolysis during this type of crisis. Occasionally, as pointed out by Clough,[3] the rate of hemolysis may increase.

During the crisis the serum iron level is usually elevated. The unchanged or low serum bilirubin concentration suggests that the high serum iron level is not due to an increase in release of iron resulting from accelerated hemolysis. Rather, it is suggested that the iron level is elevated because hemoglobin synthesis by erythroid elements is negligible during this time.

VI. Clinical Course and Treatment.—The occurrence of an erythroblastopenic crisis in a patient with a hemolytic disorder is clearly a matter of serious import. There may be such an explosive increase in the severity of the anemia that within a period of two to three days the patient may have become critically ill. During this time blood must be supplied in order to correct the severe anemia and to maintain erythrocyte and hemoglobin values above a critical level.

In the great majority of the patients the aplastic crisis is self-limited. Since it is difficult to recognize the exact time of onset, several days may elapse before the diagnosis is established; however, most patients begin to show an intense erythroblastic proliferation in the marrow within five to six days after the onset of the aplastic crisis. Marrow cultures have indicated the maturation time from pronormoblasts (early erythroblasts) to reticulocytes to be approximately four days.[27] In accordance with this observation, approximately 10 to 12 days after the onset of the crisis reticulocytes begin to appear in increasing numbers in the peripheral blood. Most cases reported in the literature seem to have followed the type

of clinical course just described, with beginning recovery from the crisis within 10 to 12 days.

To this time management has included only measures aimed at modifying or eliminating predisposing factors and general supportive therapy including the use of transfusions. The two cases in this report are among the first in whom corticotropin and adrenal corticosteroids have been used. Contopoulos' demonstration of the presence of an erythropoietic stimulating factor in the anterior pituitary [28] would make this therapeutic approach seem rational. It is hazardous to draw conclusions from such limited experience. It did seem, however, that in one of the patients (Case 1) the course was three to four days less than that of the majority of the previously reported cases. It is recommended that corticotropin and adrenal corticosteroids be used in other cases of erythroblastopenic crisis in order that the efficacy of this therapeutic regimen may be evaluated more accurately.

Summary and Conclusions

The subject of acute erythroblastopenic crisis has been reviewed from the standpoint of antecedent diseases, etiologic and predisposing factors, dynamics of erythrocyte formation and production of the crisis, clinical picture and laboratory data, and the clinical course and management.

Acute erythroblastopenia may occur as a complication of already existing hemolytic diseases, such as familial spherocytosis, sickle-cell anemia, erythroblastosis fetalis, acquired hemolytic anemia, and paroxysmal nocturnal hemoglobinuria. It may also occur in otherwise hematologically normal persons as a complication of a variety of conditions, such as allergic reactions, infections, and other miscellaneous disease processes.

Two cases of acute erythroblastopenic crises, one occurring in a patient with acquired hemolytic anemia and another in a patient with sickle-cell anemia, are reported herein.

The severity of the clinical manifestations is dependent upon the presence or absence of coexisting hemolysis. When a severe hemolytic process is present, erythroid hypoplasia results in a rapidly developing and progressing anemia. When there is no coexisting hemolysis, the anemia, if any develops, is slight and may escape detection.

Pertinent laboratory findings during an erythroblastopenic crisis include a reticulocytopenia. Leukopenia and thrombocytopenia in the peripheral blood are less constantly observed. The bone marrow at the same time reveals an erythroid hypoplasia. The serum bilirubin usually remains constant or may fall, as does the fecal urobilinogen. The serum iron is commonly elevated during the course of the crisis.

An acute erythroblastopenic crisis is usually self-limited, and recovery begins within 10 to 12 days.

The patients reported herein were both treated with supportive measures including transfusions, and in addition received corticotropin and adrenal corticosteroids. It seems possible that the course of the process in one of the patients was somewhat shorter than that in the majority of cases, with recovery beginning within five to seven days. Further use of corticotropin and adrenal corticosteroids in the management of erythroblastopenia is recommended so that its efficacy can be evaluated further.

Mrs. Elsie W. Houston and Mrs. Oleta H. Cody gave technical assistance.

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Studies on the Relationship Between the Peripheral Blood Counts and the Total Body Red Cell Volume

II. In Patients with Addisonian Pernicious Anemia in Relapse, During Recovery, and in Remission

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Introduction

It has been shown previously that in normal persons there is a relatively constant relationship between the hematocrit of peripheral venous blood and the circulating red blood cell volume per kilogram of body weight (CRBCV/kg.). In these instances the hematocrit is a useful and practical indicator of the size of the erythron. However, in patients with polycythemia vera and in certain persons in whom the peripheral hematocrit is abnormally high, this relationship was found to be unreliable.[1] The ratio, hematocrit of peripheral venous blood divided by CRBCV/kg. $\left(\frac{\text{Hct.}}{\text{CRBCV/kg.}}\right)$, gives an indication of the relative error of the hematocrit which may be spuriously normal, elevated, or low.

In the present study this relationship was determined in patients with Addisonian pernicious anemia in relapse, during regeneration in response to specific therapy, and in remission. It was found in patients who were in hematologic relapse that the venous hematocrit correlated poorly with the CRBCV/kg. and therefore during therapy, was an unreliable guide to the actual total body hemoglobin regeneration.

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Miss Rosalie Lesser and Miss Mildred Fishman gave technical assistance.

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Materials and Methods

Of the 13 patients with Addisonian pernicious anemia who form the basis of this report, measurements were made on 6 while they were in hematologic relapse. In four, the studies were repeated after vitamin B_{12} therapy had been instituted and erythrocyte regeneration was in progress but before normal blood values were reached. Seven patients were selected from the hematology clinic. They had been receiving maintenance therapy for prolonged and variable periods and were considered to be in a stable hematologic remission. Three of these were selected because they were found to have abnormally high hemoglobin values. In all patients, measurements were made of the hemoglobin concentration, red blood cell count, and hematocrit of the peripheral venous blood, employing standard acceptable techniques.[2] The determination of the circulating red blood cell volume was performed utilizing erythrocytes tagged isotopically with P^{32}, as described earlier.[3] In one patient the plasma volume was also determined simultaneously, using human serum albumin tagged isotopically with I^{131}. The method used was similar to that described by Berson and Yalow.[4] The diagnosis of Addisonian pernicious anemia in all of these subjects was established by the usual clinical criteria. This was confirmed by demonstration of an absence of endogenous intrinsic factor activity, using the urinary excretion test previously described.[5]

Results

The observations made are recorded in the Table. In the first four instances measurements were made before and during blood regeneration following therapy. It is of interest to compare the per cent increase in the values determined from samples of venous blood (hemoglobin, hematocrit, and

Addisonian Pernicious Anemia

Patient	Sex	Age, Yr.	Weight, Kg.	Hct., %*	CRBCV, Ml.†	CRBCV/Kg., Ml.‡	Ratio Hct./CRBCV/Kg.§	Status
K.K.	F	57	50. 47.7	21. 30.	490 685	9.8 14.4	2.14 2.08	Relapse During regeneration
S.W.	F	60	63.4 56.8	16. 25.	683 1243	10.8 21.9	1.48 1.14	Relapse During regeneration
L.C.	F	63	44.5 50.	20. 29.5	934 1500	20.9 30.	.96 .98	Relapse During regeneration
J.H.	M	68	62.7 59.8	26.5 35.	1168 1416	18.6 23.7	1.424 1.48	Relapse During regeneration
J.C.	F	84	48.6	13.	300	6.2	2.11	Relapse
M.L.	F	80	43.6	23.	1029	23.6	.97	During regeneration
F.S.	F	51	61.4	41.5	1336	21.8	1.90	Maintenance therapy
L.S.	M	76	68.2	53.	2066	30.4	1.74	Maintenance therapy
E.E.	M	59	78.6	48.	2378	30.3	1.58	Maintenance therapy
S.S.	M	65	70.5	51.	2257	32.0	1.59	Maintenance therapy
F.M.	M	72	56.4	44.5	1853	32.8	1.36	Maintenance therapy
S.R.	M	55	57.2	54.	2589	45.3	1.19	Maintenance therapy
J.T.	M	72	90.5	52.5	2294	25.3	2.08	Maintenance therapy

*Peripheral venous hematocrit.
†Circulating red blood cell volume.
‡Circulating red blood cell volume per kilogram of body weight.
§Hematocrit divided by circulating red blood cell volume per kilogram of body weight.

red blood cell count) with the changes in the whole body hemoglobin content and red blood cell volume. In Patient K. K. there was a very good correlation between these values (Fig. 1). For example, the magnitude of the change in peripheral hematocrit (+42.8%) is essentially the same as the increase in the circulating red cell mass per kilogram of body weight (+47.6). This is reflected in the ratio of Hct/CRBCV/kg., which did not change before and after therapy. The ratio in this instance was persistently high, i. e., 2.1. The normal ratio ranges from 1.3-1.6.[1] The hematocrit here is unreliable in reflecting the true severity of the anemia, although the change in hematocrit did accurately reflect the changes in the total quantity of erythrocytes in the body.

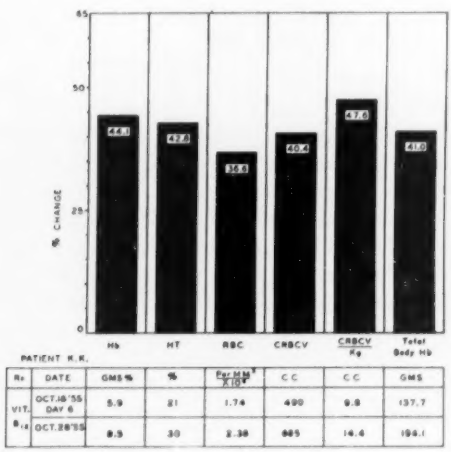
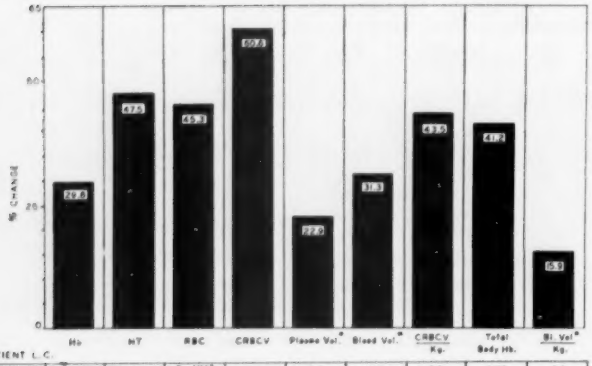


Figure 1

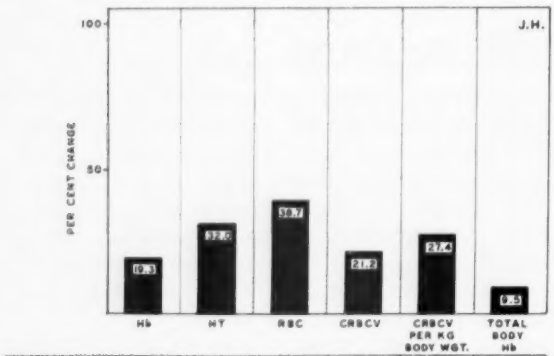
In Patient L. C. a good correlation was also noted in the per cent change in peripheral blood values with total body measurements (Fig. 2). For example, the peripheral hematocrit increased 47.5% while the CRBCV/kg. increased 43.5%. Again, the ratio of Hct/CRBCV/kg. did not change significantly (0.96-0.98). In this instance, however, the ratio is abnormally low. Here the peripheral hematocrit exaggerates the severity of the anemia. It is of interest that the hematocrit measurements and the weights of these two patients were essentially the same before and during regeneration, yet Patient L. C. had a circulating red cell volume per kilogram that was more than twice as large as that of Patient K. K. (Table). In Patient J. H., where a good correlation was noted between the per cent



PATIENT L. C.

Rx	DATE	GMS %	%	Per MM³ X 10⁶	CC	CC	CC	CC	GMS	CC
VIT. B_{12}	OCT. 17 '55 DAY 1	8.7	28	1.80	934	3250	4184	20.9	313	94.0
	OCT. 31 '55 DAY 15	8.7	29.5	2.76	1500	3885	5495	30.0	442	109.9

Figure 2



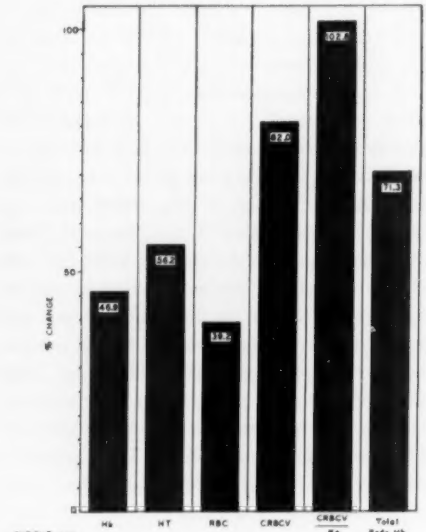
RX	DATE	GMS %	%	PER MM³ X 10⁶	CC	CC	GMS
VIT. B_{12}	FEB. 14, 1956 DAY 2	8.8	26.5	2.25	1168	18.6	388
	MARCH 1, '56 DAY 16	10.5	35	3.12	1416	23.7	425

Figure 3

change in the peripheral hematocrit and the CRBCV/kg., a persistently normal ratio of Hct/CRBCV/kg. was found (Fig. 3). In this instance the hemoglobin, hematocrit, and red blood cell count truly reflect the magnitude of both the initial circulating red blood cell volume and the increase in this volume following vitamin B_{12} therapy.

Patient S. W., studied similarly, differed in that the correlation between the per cent increase in the peripheral blood and the total body blood values was poor (Fig. 4). For example, the hematocrit increased 56.2% while the CRBCV/kg. increased 102.8%. Here the ratio of Hct/CRBCV/kg. before therapy was normal, 1.48. During regeneration it fell to 1.14. The increase in the circulating red blood cell volume per kilogram is not fully reflected by a concomitant rise in the venous hematocrit.
a hematocrit of 53.0%, and J. T., with a

In the two other patients who were studied, J. C. during relapse and M. L. during regeneration, the ratios of Hct/CRBCV/kg. were 2.1 and 0.97, respectively. Both of these values are abnormal. The hematocrit



PATIENT S.W.

B_{12}	DATE	GMS %	%	$\frac{Mill/mm^3}{X\ 10^6}$	CC	CC	GMS
VIT.	DEC. 20'54 DAY 7	4.9	18	1.76	683	10.8	209
B_{12}	JAN. 4'55 DAY 22	7.2	25	2.45	1243	21.9	358

Figure 4

in the former is "too high" and in the latter it is "too low."

The remaining seven patients studied were receiving maintenance therapy with vitamin B_{12} and were attending the hematology clinic.

Patient F. S., whose peripheral blood values were normal (hematocrit, 41.5%), was found to have a low CRBCV/kg. (21.8 ml/kilogram). The ratio therefore was abnormally high, i. e., 1.90. L. S., with hematocrit of 52.5%, had normal values for CRBCV/kg. The ratios here were therefore elevated. These patients were included in the group described as "Plethora" in a previous publication.[1] E. G., S. S., and F. M. were normal in all respects. S. R. proved to have an elevated CRBCV/kg. and a high venous hematocrit. The low ratio Hct/CRBCV/kg. (1.19) was similar to that found in many patients with polycythemia vera.[1] In Figure 5 the relationship between the peripheral hematocrit and the circulating red blood cell volume per kilogram body weight is charted. Note that the ratio varies widely in patients with pernicious anemia as compared to the normal control group.

Comment

Determinations of the blood volume in patients with Addisonian pernicious anemia have been made previously.[6-11] The results have been inconstant, so that no generalizations have been possible. This is understandable for various reasons. First of all, since the severity of the disease varies

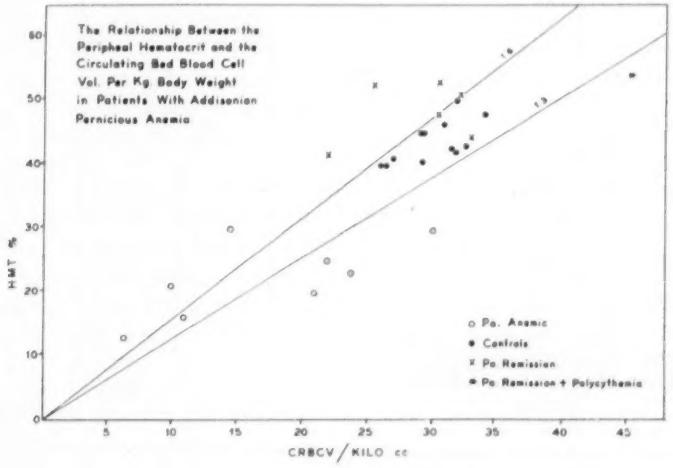


Figure 5

from patient to patient one would expect concomitant variations in the size of the erythron. Therefore, in these patients, any correlation of the size of the CRBCV with normal values must, by necessity, be inconstant. Secondly, in some of the reports, plasma protein tagging methods, such as Evans blue dye (T1824) or I^{131}-labeled albumin, were employed. Isotopically labeled red cells were used by others. In abnormal states, such as Addisonian pericious anemia, the use of either of these methods alone for the determination of whole blood volume is subject to error, since a constant relationship between the plasma and red blood cell volume does not exist throughout the body. Because of the difference between the average body hematocrit and the peripheral vessel hematocrit, the accurate evaluation of the whole blood volume requires independent determinations of plasma and red blood cell volume.[12] Conclusions drawn from methods employing isotopically tagged red cells alone should be confined to the circulating red blood cell volume. Conversely, when plasma-protein-tagging methods are used, only conclusions concerning plasma volume are possible.

In the normal state the peripheral blood cell counts reasonably reflect the total volume of red blood cells in the body (when corrected for weight). This correlation cannot be consistently carried over to persons with polycythemia vera or with elevated peripheral blood cell counts.[1] The present study indicates that this correlation also fails in patients with pernicious anemia. Here the clinical state may more truly reflect the size of the circulating red blood cell mass than the hematocrit. Patients with pernicious anemia are seen who are similar in regard to weight, body configuration, and degree of anemia as estimated by the peripheral venous hematocrit. However, the CRBCV/kg. may vary greatly. In some instances the hematocrit underestimates the red blood cell volume deficit. The variability of the CRBCV/kg. in relation to the hematocrit is noted in Figure 6.

In evaluating the response of a patient with Addisonian pernicious anemia to specific therapy it is customary to note the progressive rise in peripheral blood cell counts. When the red blood cell count, hemoglobin, and hematocrit cease to rise or lag behind the expected responses we usually consider either a failure of the therapeutic agent or the development of a complication such as infection. However, in the present study it was noted that one patient actually

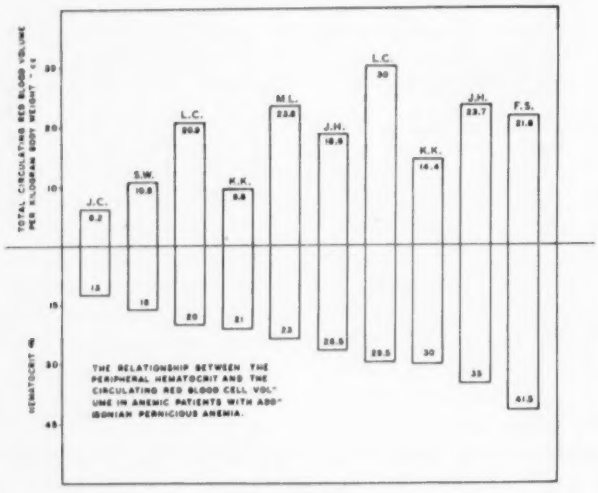


Figure 6

doubled her total body red blood cell volume while only showing a 50% rise in peripheral venous blood. Therefore during regeneration the peripheral red blood cell counts may be misleading.

Patients with pernicious anemia who have been treated with parenterally administered extrinsic factor for prolonged periods of time are usually assumed to be hematologically restored to normal. Of the four such patients selected from the hematology clinic, one was found to have a slightly low circulating red blood cell mass per kilogram body weight. The remaining three were selected because of high peripheral venous hematocrits. Two of these patients had normal values for the CRBCV/kg., while the third had a CRBCV/kg. of 45.3 cc/kilogram, which is distinctly elevated and well within the range of absolute polycythemia.

No definite conclusions can be made from this study concerning the frequency of abnormally high or low circulating red blood cell volumes in patients with Addisonian pernicious anemia in remission. Only a few cases were studied, and they were not selected in a random fashion. However, these results do suggest that the hematologic status is not always normal in patients with Addisonian pernicious anemia in remission following prolonged vitamin B_{12} therapy. A more extensive study of such a group seems indicated.

Summary and Conclusions

Thirteen patients with Addisonian pernicious anemia were studied by determining the circulating red blood cell volume, using isotopically tagged red blood cells.

A poor correlation between the peripheral venous hematocrit and the circulating red blood cell volume per kilogram body weight was found in patients with pernicious anemia in relapse and during regeneration. In some instances the venous hematocrit was "falsely high," and other times, "falsely low." In a few selected cases this poor relationship was also found in patients with Addisonian pernicious anemia during remission.

The data indicate that the degree of blood regeneration in response to specific therapy cannot always be estimated by the changes in peripheral blood cell counts. The hematologic response as determined by changes in CRBCV/kg. of body weight may be greater than that indicated by the changes noted in the venous blood. In some persons the clinical state seems to be as useful a guide in evaluating the response to therapy as is the estimation of the red blood cell volume.

Patients with Addisonian pernicious anemia in remission following prolonged vitamin B_{12} therapy may not be hematologically normal. Further investigation to establish the frequency of this abnormality seems indicated.

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Case Reports

Fatal Atherosclerotic Encephalomalacia in a Young Man

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Vascular lesions of atherosclerosis are frequently noted in young persons. These lesions, although small, may assume clinical importance when they occur in certain strategic locations. Attention has been called to the significant incidence of myocardial infarction in young men.[1,2] Encephalomalacia subsequent to atherosclerosis of the cerebral vessels, however, appears to be a distinctly rare occurrence in patients below the age of 40, and few autopsy reports are available.

Report of Case

A 28-year-old white man, a warehouse worker, was well until the morning of May 12, 1955, when he developed a slight right temporal headache. He performed manual labor throughout the day and that evening suddenly experienced marked dizziness associated with an increase in the right temporal pain. Within a few minutes he developed complete paralysis of the left arm and leg as well as slurring of speech. He was admitted to a local hospital.

Fifteen years previously the patient had had malaria. It was reported that his blood pressure had been elevated on several occasions, but this could not be verified. The past history was otherwise not contributory.

Physical examination showed a blood pressure of 144 mm. of mercury systolic and 80 mm. diastolic and a pulse rate of 84 per minute. The pupils were dilated and equal. The retinal vessels were unremarkable, and there was no choking of the optic discs. Nystagmus and a left hemiparesis including the muscles of the face and tongue were present. The tendon reflexes on the left were slightly hyperactive, with a positive left Babinski reflex. Perception of light touch was absent, and vibratory and pain sensations were diminished on the left. The physical examination was otherwise within normal limits.

Cerebrospinal fluid obtained the day after admission was under an initial pressure of 166 mm. of water and contained 10 lymphocytes and total protein of 24 mg. per 100 cc. The Wasserman and colloidal gold curve were negative.

Nausea and vomiting appeared two days after admission, and he was transferred to Emory University Hospital in coma. The blood pressure was 160 mm. of mercury systolic and 90 mm. diastolic, pulse rate 50 per minute, and respirations 20 per minute. Additional physical findings were a constant straight-ahead stare without nystagmus, dilated right pupil and constricted left pupil, absent light reflexes, and bilaterally positive Babinski reflexes. The lungs were filled with rales and rhonchi. An urinalysis was normal except for a 1+ proteinuria.

Treatment consisted only of supportive measures. Seven hours after admission spontaneous respirations suddenly stopped. He was maintained in a respirator but died 72 hours after the first appearance of hemiplegia.

Autopsy Findings.—Autopsy was performed 12 hours after death. The findings of major interest were in the brain, which weighed 1775 gm. Marked edema with flattening of the convolutions, a pronounced cerebellar pressure cone, and extensive compression of the medulla were present. The cerebral hemisphere and cerebral peduncle on the right were enlarged, with displacement of the optic chiasm downward and to the left. The right parietal lobe was soft to palpation. On cut section a large irregular area of encephalomalacia, 4.5 cm. in diameter, was found on the right side, involving the internal and external capsule, putamen, and globus pallidus. The thalamus was spared. There was softening of the gray matter in the posterior part of the Sylvian fissure and insula. The pons contained two irregular foci of recent hemorrhage, each measuring 0.5 cm. in greatest diameter.

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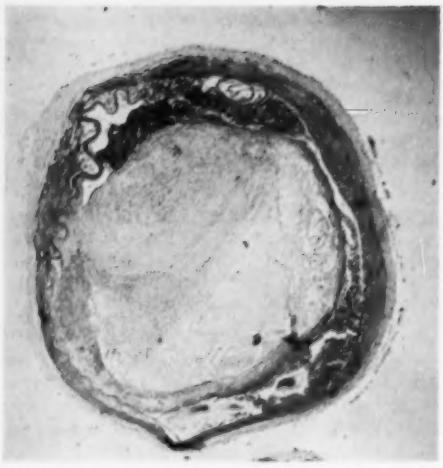


Fig. 1.—Cross section of right middle cerebral artery. An atherosclerotic plaque encroaches upon the lumen, with recent hemorrhage between media and plaque (right lower corner). A recent thrombus (top left) occludes the residual lumen; hematoxylin-phloxine; × 30.

Examination of the cerebral vessels showed an atheromatous plaque in the right middle cerebral artery just distal to the first striate branch, with a thrombus occluding the lumen and extending into the remaining striate branches. The internal carotid arteries and the other vessels of the circle of Willis were patent and free of atheromatous plaques, thrombi, and anomalies. On histologic examination, the area of gross infarction showed necrotic brain tissue with some polymorphonuclear leukocytic infiltration. Other regions of the brain showed marked edema. Multiple sections of the right middle cerebral artery through the area of occlusion showed marked intimal proliferation with hyalinization, splitting and fraying of the elastic lamellae, and cholesterol deposits (Figs. 1 and 2). There was no inflammation of the wall of the artery. Subintimal hemorrhage had dissected the intima from the media for a distance of several centimeters, finally rupturing into the lumen. A recent thrombus occluded the lumen.

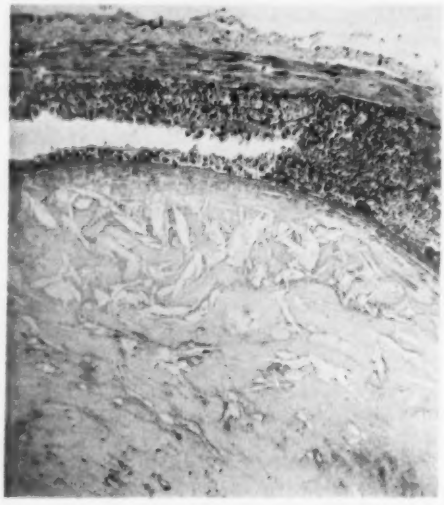
Significant findings in other organs included marked pulmonary edema and atelectasis of both lower lobes of the lungs, acute congestion of the viscera, and a follicular adenoma of the thyroid. A few atheromatous streaks were seen in the coronary arteries near their origin and in the intima of the aorta. The heart was of normal weight (345 gm.). There was no arteriolar thickening or hyalinization in the other organs.

Anatomic Diagnoses: Atherosclerotic plaque of the right middle cerebral artery with hemorrhage and thrombosis producing encephalomalacia of the right parietal lobe and basal ganglia. Cerebral edema. Pontine hemorrhages. Atherosclerosis, minimal, coronary arteries and aorta. Pulmonary edema and atelectasis. Congestion of viscera, acute. Follicular adenoma of thyroid.

Comment

This patient, a 28-year-old manual laborer, died 3 days following the onset of hemiplegia. At autopsy he was found to have extensive encephalomalacia of the basal nuclei and parietal lobe on the right caused by hemorrhage into an isolated atherosclerotic plaque of the right middle cerebral artery with subsequent thrombosis. Except for the single plaque, the cerebral vessels were free of atherosclerosis, and only minimal atherosclerotic changes were found in the coronary arteries and aorta. There was no evidence of a local inflammatory or congenital lesion and no clinical or morphological evidence of syphilis. No trauma to the head had occurred. Although an unverified history of transient hypertension was obtained, a sustained hypertensive state was considered unlikely in view of clinically normal retinal vessels, the normal heart size, and the absence of arteriolar sclerosis in all organs.

Fig. 2.—Same as Figure 1, showing hemorrhage between media and atherosclerotic plaque; hematoxylin-phloxine; × 90.



Ross [3] summarized the neuropathologic material at Bellevue Hospital up to 1946 and found no proved instances of cerebral vascular occlusion in the absence of hypertension, syphilis, or arterial embolism below the age of 55. Included in his series, however, were six patients who recovered following what appeared on clinical grounds to have been an atherosclerotic occlusion of cerebral vessels. More recently, Berlin and co-workers [4] called attention to the frequency of cerebral thrombosis in the age group below 40 when they reported 13 cases, including a 28-year-old man who died following thrombosis of the basilar artery with pontine degeneration. The vessel showed fibrous thickening of the intima, with hemorrhage into the wall dissecting the intima from the media. Kennedy and co-workers [5] mention a 32-year-old normotensive man who had 14 attacks of right-sided hemiplegia within an eight-week period, from which recovery was complete in all except the last episode. Premature cerebral atherosclerosis was recorded at autopsy, but detailed description was not given. In a review of 100 autopsied cases of spontaneous vascular encephalopathy, Irish [6] found 17 instances of vascular thrombosis below 40 years of age, but only 1 of these was arterial. Ford and Schaffer [7] cited 43 instances of acquired hemiplegia in childhood among 50,000 admissions to the Harriet Lane Home, in Baltimore. An arterial thrombosis with cerebral infarction was found at operation in one child, and autopsy of another showed thrombosis of the middle cerebral artery just distal to the striate branches, with cortical encephalomalacia. Atherosclerotic plaques were present in all cerebral arteries. Occlusion of cerebral arteries and subsequent encephalomalacia have also been noted following trauma [8-10] and may be associated with dissecting aneurysms of these vessels.[11]

Encephalomalacia in the absence of cerebral vascular lesions has been described.[12] Recent emphasis has been placed upon the importance of thrombosis of the internal carotid artery as a cause of hemiplegia in such patients. Johnson and Walker [13] found 101 reported cases and added 6. Thirty-five of the patients were below the age of 40. Gurdjian and Webster [14] saw 30 patients with this disorder in a four-year period, including seven below the age of 40. The thromboses were all on the basis of atherosclerosis.

Encephalomalacia associated with atherosclerosis of the cerebral vessels is infrequent in young persons. The literature on this subject is difficult to evaluate, since many clinical and morphologic entities are included, but cerebral atherosclerosis was shown to be the underlying lesion in only three instances.[4,5,7] In the patient presented, encephalomalacia could be clearly related to hemorrhage into an isolated atherosclerotic plaque of a middle cerebral artery.

Summary

Hemorrhage into an isolated atherosclerotic lesion of the right middle cerebral artery was found at autopsy to be the cause of encephalomalacia in a 28-year-old laborer. The remaining cerebral vessels were normal, and only minimal atherosclerosis was noted in the aorta and coronary vessels. A review of the literature emphasizes the rarity of clinically significant cerebral artery atherosclerosis in the younger age group.

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Marfan's Syndrome with Aortic Thrombosis

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In 1896 Marfan[1] described a congenital condition which is now commonly known as arachnodactyly, a term originally suggested by Achard, in 1902.[2] Currently, Marfan's syndrome may include, in addition to arachnodactyly, dislocation of the lenses, cardiovascular abnormalities, and skeletal defects. Although many cases show a strong familial tendency, McKusick[3] notes that 15% are *de novo* mutations. The commonest features of this syndrome are increased height, lengthening of the long bones, decreased subcutaneous fat, underdeveloped musculature, relaxation of the ligaments, kyphosis or scoliosis, sternal deformities, such as pectus excavatum, prominent ears, arched palate, subluxation of the lens in 50% to 80% of the cases, and cardiovascular abnormalities. Although the most unequivocal signs are arachnodactyly and subluxation of the lenses, the prognosis of the patient is determined by the cardiovascular lesions. The syndrome is an abiotrophy in which one or more of the traditional signs may be absent or so trivial as to escape notice.[3] A wide variety of cardiovascular abnormalities may occur in this condition. Patent foramen ovale, patent ventricular septum, patent ductus arteriosus, aortic lesions, and numerous other defects have been noted. Earlier reports stressed patent foramen ovale as the commonest cardiovascular abnormality.[4,5] Recent studies,[3,6,8] however, indicate that the aorta is the most frequently affected structure. The commonest lesion appears to be medial necrosis. The resulting weakness of the aortic wall is manifested either by dilatation of the ring with aortic insufficiency or by dissecting aneurysm. It has been suggested that this process is similar to Erdheim's medial necrosis.[9,10]

The case to be presented exhibited the gracile habitus and dislocated lenses usually associated with Marfan's syndrome. However, the fingers were not unusually elongated. In addition there was a picture of aortic obstruction.

Report of Case

The patient, a 34-year-old bookkeeper, was admitted to Bay Pines VA Center, May 7, 1955, with a chief complaint of pain in the left eye of one day's duration. On the day of onset he was told by an ophthalmologist that he had glaucoma with dislocation of the left lens. He gave a history of hypertension for 10 years. In 1948, a bilateral sympathectomy was performed in an unsuccessful attempt to relieve this condition. Myocardial infarction occurred in 1951. Since 1951, he noted progressive impairment of vision bilaterally. His mother and father are second cousins and are living and well. Neither the parents nor his five siblings show the stigmata of Marfan's syndrome. In addition to bilateral sympathectomy the patient had surgery in 1948 for intestinal obstruction due to adhesions.

Physical Examination.—The patient is a white man, with height 6 ft. 2 in., weight 165 lb., temperature 98.4 F, and pulse 80. Blood pressure in both arms was 190/90; blood pressure was too feeble to obtain in both legs. Eyes, left vision 20/300, right 10/300, both uncorrected. Slit-lamp examination shows dislocation of both lenses. Both retinae show vascular sclerosis. Ears, nose and throat, and lungs are negative. The abdomen presents scars from bilateral sympathectomy. A prominent aortic thrust is felt down to 1 in. above the umbilicus. The femoral pulses are weak bilaterally. The left popliteal pulse is feeble, and the right is not palpable. No pulses are felt in the feet. There is no gross evidence of collateral circulation.

Laboratory Data.—WBC, 5300; RBC, 3.78 million; corrected sedimentation rate, 12; V. D. R. L., negative. Routine chest film shows the heart and lungs to be within normal limits. There is no notching of the ribs such as is usually seen with coarctation of the aorta. An intravenous pyelo-

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From the Veterans Administration Center, Bay Pines, Fla.

gram demonstrates a double set of kidney pelves and calyces on the right. Both renal pelves are dilated. There is narrowing of the aorta above the third lumbar level, but decreased diameter of the thoracic aorta is not demonstrable.

The patient was transferred to the Veteran's Administration Hospital, Durham, N. C., for further study. An aortogram showed complete block below the renal arteries, suggesting Leriche's syndrome. On June 22, 1955, the thrombosed aortic segment was excised and replaced with an aortic homograft.

Comment

The coexistence of a tall, gracile habitus and dislocated lenses is compatible with Marfan's syndrome in its current implication of a widespread abiotrophy involving several systems in a characteristic but not uniform fashion. Thus, in this case, while the skeletal, ocular, and vascular systems were involved, arachnodactyly was not conspicuous. Although Marfan originally described arachnodactyly only, modern students of this complex, such as McKusick, stress the importance of dislocated lenses as the least equivocal component of the syndrome. Moreover, aortic complications should be suspected in all cases of ectopia lentis. As in many cases of Marfan's syndrome, the aorta was the site of disease, the condition here being thrombotic occlusion, or Leriche's syndrome.[9] This is evidently a rare complication of Marfan's syndrome, for it was not listed in reviews of previously collected cases.[3,4,10] The underlying pathologic factors which predispose to aortic thrombosis in a young person are not clear. Shapiro[12] lists the possible causes of thrombotic occlusion of the aorta as follows: 1. Ulcerated arteriosclerotic plaque; 2. arteritis; 3. dissecting aneurysm; 4. narrowing of the aorta, congenital or acquired. Aortic thrombosis tends to occur in persons older than our patient. The relationship of this patient's hypertension to the aortic occlusion is a matter for conjecture, since the precise time of onset of these conditions is unknown. The absence of similar defects in other members of the family suggests that this is a *"de novo* mutation."[3]

Marfan's syndrome with partial aortic obstruction has been reported in a few cases, but these were due to narrowing of the aorta[10,11] rather than to thrombosis.

Summary

A case is presented showing several of the congenital defects of Marfan's syndrome. This case is unusual in that it was complicated by thrombotic occlusion of the abdominal aorta.

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Pregnancy and Successful Delivery in a Case of Tetralogy of Fallot

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Patients with congenital cyanotic heart disease and pregnancy have been classified as "unfavorable risks."[1-3] Thus, according to some authorities,[1-4] they should be aborted in the first trimester. With the development of special surgical techniques in diagnosis and surgery over the past 15 years, patients with congenital heart disease who formerly died are now in the child-bearing age and may continue with pregnancy safely. The question of how well these patients tolerate pregnancy has not been satisfactorily established, and the accepted prognosis may have to be revised.

Very few cases of normal pregnancy and successful delivery in surgically treated tetralogy of Fallot have been reported in the literature. However, there are probably other cases not reported at present. The following case report is submitted, and we hope that others will also publish their experience, so that a significant series will permit a better study of this problem.

Report of Case

A 20-year-old Negro woman had been followed in our medical outpatient department for several years because of a twice-operated-on tetralogy of Fallot. Although, she had been advised not to become pregnant, she presented herself at eight weeks' gestation. It was decided not to interrupt pregnancy. She did well until the 29th week of gestation, when she was admitted to the hospital because of severe abdominal pain and onset of fatigue and dyspnea.

At the age of 9, a surgical correction of a severe tetralogy of Fallot was attempted. Because of the small size of the pulmonary artery, a small branch of the aorta was anastamosed to the left pulmonary artery. This procedure proved to be unsatisfactory, and a right Blalock operation was performed five years later with excellent results.* The patient, previously bedridden, slowly resumed a more normal life, and her physical development rapidly improved. A slight cyanosis and dyspnea with moderate to severe exertion persisted. She also remained quite retarded mentally. Since that time, she has been well except for an appendectomy done under local anesthesia, which was well tolerated. The systemic review did not reveal any other significant symptoms.

She has one brother, who is well. Her mother and father are living and in good health.

The physical examination revealed a well-developed Negro woman, lying flat in bed without dyspnea. Blood pressure was 140/90 in both legs. Pulses and blood pressure were unobtainable in both arms. There was definite cyanosis of the oral mucosa and finger nailbeds. The neck veins were not distended. The chest was clear to auscultation and percussion.

The right heart border was percussed at 3 cm. to the right of the midsternal line in the fourth interspace. The left heart border was at the midclavicular line. A continuous murmur was heard in the second left interspace at the left sternal border with a harsh systolic component. The pulmonic second sound was greater than the aortic second sound. The heart rate was 80 per minute, with a normal sinus rhythm.

Abdominal examination was negative except for an enlarged uterus, compatible with 29 weeks' gestation. The uterus was quite irritable. The head was floating. Pelvic examination revealed no effacement or dilatation of the cervix.

There was minimal clubbing of the fingers and toes. There was no peripheral edema.

A complete blood cell count revealed 5.3 million red blood cells, a hemoglobin of 16.4 gm. per 100 cc., and a hematocrit of 56 mm. White blood cell count and differential were normal. On repeated urinalysis there was 0-2+ albuminuria. Microscopic examination was negative. The chest x-ray disclosed a normal heart size, with a prominent pulmonary artery segment and a right-sided

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* Surgery done by Dr. F. D. Dodrill.

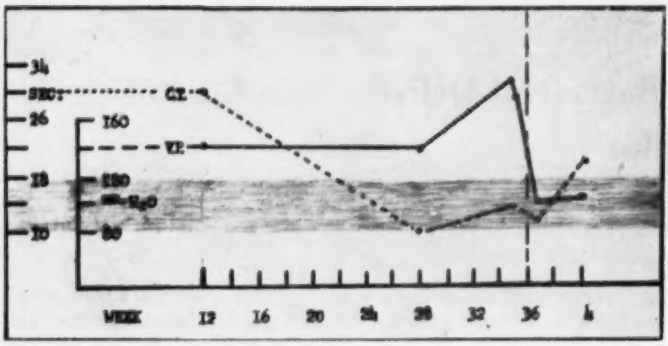

Fig. 1.—Venous pressure in centimeters of H_2O. Arm-to-tongue dehydrocholic acid circulation time in seconds. Note the significant rise in the venous pressure at the 28th week and the fall to normal after delivery.

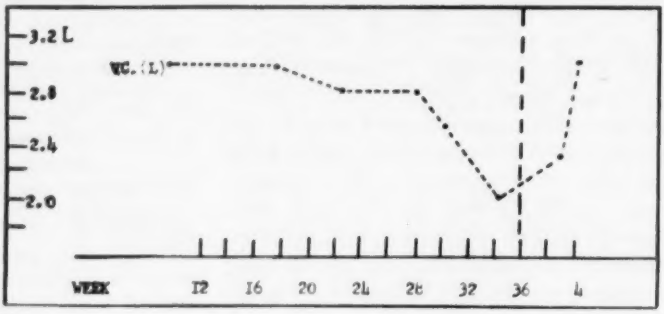

Fig. 2.—Total vital capacity in liters. Observe the significant fall beginning at the 28th week and the postpartum return to normal.

aorta. At fluoroscopy, the pulmonary arteries were pulsatile. The electrocardiogram showed a vertical heart, with right ventricular hypertrophy.

The patient was given a 200 mg. low sodium diet and remained at complete bed rest until delivery, seven weeks later. She did not develop symptoms or physical signs of congestive heart failure. Vital capacity, circulation time, and venous pressure studies were determined at regular intervals (Figs. 1 and 2). The changes in the vital capacity and venous pressure did suggest a latent cardiac insufficiency approximately four weeks before delivery. The patient was slowly digitalized.

She had repeated episodes of impending labor during the remainder of her antepartum period. Uterine irritability was controlled by small doses of intramuscular meperidine (Demerol). A 15 lb. weight gain was recorded during the pregnancy.

She went into labor at 36 weeks' gestation. Analgesia was maintained with 20 mg. of intravenous meperidine and a pudendal block. The membranes were ruptured artificially, and a right occiput posterior was converted by manual rotation to a right occiput anterior. With the aid of a left mediolateral episiotomy and a short DeLee forceps application she was delivered of a normal, vigorous 4 lb. 12 oz. boy. The total duration of labor was 2 hours 37 minutes. Oxytocics were not used at any time. Oxygen by mask was given during the entire labor and delivery period.

The pulse rate rose to 120 per minute during labor, and the blood pressure was recorded at 90/70 in the right leg following delivery. There was no evidence of shock or congestive failure. Blood loss was estimated at 200 cc. Four hours later the pulse rate was 96 per minute and the blood pressure was 110/80. Oxygen therapy was continued during the following three days, and ambulation was begun one week post partum. The mother and infant were discharged two weeks after delivery in good condition.

As shown in Figures 1 and 2, the vital capacity, blood volume, and venous pressure slowly returned to previous levels. Comparative studies of the heart by chest x-ray and electrocardiogram taken before and after pregnancy did not show any significant increase in the heart size.

Comment

Only three cases of operated-on tetralogy of Fallot and pregnancy have been previously reported. One was a case [5] of an 18-year-old Mexican who was delivered of an apparently normal girl. Pregnancy, delivery, and postpartum course were normal,

and her cardiac status was essentially unchanged by the pregnancy.

The second case [6] was of a 19-year-old white woman who had been delivered of an anencephalic fetus at six and one-half months' gestation. Fifteen months after a Blalock procedure she was delivered of a normal girl. Pregnancy, delivery, and postpartum course were uneventful.

The third case [7] reported was a 25-year-old unipara who had an essentially normal pregnancy and low-forceps delivery of an erythroblastotic baby. Postpartum course was normal. The baby was given an exchange transfusion and survived.

A fourth case [8] of cyanotic heart disease, possibly tetralogy of Fallot, was in a 26-year-old woman who had no mention of previous corrective surgery and had an apparently normal pregnancy and delivery.

Definite conclusions cannot be drawn from the study of such a small number of cases. It may suggest that the prognosis of pregnancy in surgically treated tetralogy of Fallot may not be as unfavorable as previously thought and that normal pregnancy and delivery may be expected. However, this optimism should not jeopardize the careful management of these cases.

These patients should be checked frequently, with special emphasis on controlled weight gain and latent symptoms and signs of congestive heart failure. Vital capacity, circulation time, and venous pressure recordings should be done at frequent intervals.[1] Since toxemia is such a serious problem in the pregnant cardiac,[3,9] blood pressure and urinalysis should also be followed closely.

Oxygen should be administered during labor and delivery [1] and in the immediate postpartum period until the patient's blood volume returns to a more physiologic level.

Local anesthesia, either caudal or pudendal block, is safe and satisfactory.[1] Small doses of meperidine may be used for analgesia.

During delivery, hypotention should be avoided to prevent reversal of shunt. Apparently this complication was the cause of death in a few cases of patient ductus arteriosus.[10] Methods such as binding and elevating legs may be used to combat hypotention.[10] Vasopressor drugs may also be used. The second stage of labor should be shortened by the use of forceps and episiotomy.[1]

Antibiotics are an important prophylaxis against subacute bacterial endocarditis, which is a serious threat at the time of delivery and during the postpartum course.[10]

With the above precautions, many pregnant patients with surgically treated congenital heart disease may have a normal gestation and successful delivery, as illustrated by these cases. Certainly, many cases will not follow this pattern, and their management will continue to pose most difficult and complex problems.

Except for the marked uterine irritability which necessitated hospital care for a period of seven weeks prior to delivery, this patient did not present other significant difficulties. The uterine hyperirritability and premature onset of labor are common in the pregnant cardiac patients. One series reports an incidence of premature labor of 22%.[3]

Although no clinical signs of congestive failure were observed at any time, the disproportionate fall of the vital capacity and the rise of venous pressure during the third trimester (Figs. 1 and 2) suggested a latent failure which constituted an indication for digitalis therapy. The drop of the dehydrocholic acid (Decholin) circulation time in the low normal range in the face of an elevated venous pressure may be due to an increased right-to-left shunt, which is also suggested by the increased cyanosis during the later part of gestation.

A moderate hypotension without evidence of shock occurred at delivery with rapid and spontaneous recovery. A slow intravenous drip of 5% dextrose in water was used during delivery and the postpartum period so that arterenol could be added in case true shock developed.

Summary

A case of surgically treated tetralogy of Fallot with pregnancy, delivery, and uneventful postpartum course is presented.

A review of the literature reveals that three similar cases have previously been reported.

It is suggested that patients with surgically treated tetralogy of Fallot and possibly other cyanotic heart diseases may have normal pregnancy and successful delivery. The essential problems of management are briefly discussed.

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Books

EDITED BY WILLIAM B. BEAN, M.D.

BOOK REVIEWS

Säuglings-Enteritis. Edited by Dr. A. Adam. Price, $14.30. Pp. 534, with 36 illustrations. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart N, 1956.

According to the authors of this book, a change in views has taken place in recent years concerning the etiology and therapy of diarrheic diseases in infants. They feel, in contrast to other competent men, that the emphasis in these conditions should be put on infection.

An attempt is made to clarify the international nomenclature of this important chapter in pediatrics, which up to now, has shown some confusion in the Anglo-Saxon, French, and German literature.

The proposed terms are "primary enteritis" when the pathogenous germs have invaded the intestines directly and "secondary enteritis" if the source of infection is parenteral. "Dystrophy" is the suggested term for states following either infection.

The scope of the book unfolds in the number of pages dedicated to the various topics:

(1) Bacteriology of Escherichia Coli-Enteritis, by Drs. F. Kaufmann and F. Ørskov, Copenhagen, 40 pages

(2) Salmonella-Enteritis, by Dr. E. F. Schmidt, Rostock, Germany, 38 pages

(3) Epidemiologie of Infant-Enteritis, by Dr. O. H. Braun, Erlangen, Germany, 82 pages

(4) Pathological Anatomy of Infant-Enteritis, by Dr. G. Ilgner, Erlangen, Germany, 56 pages

(5) Water-Balance and Mineral-Metabolism, by Dr. H. Hungerland, Giessen, Germany, 50 pages

(6) Protein and Carbohydrate Metabolism in Interitis, by Dr. K. Schreier, Heidelberg, Germany, 65 pages

(7) Protein and Carbohydrate Metabolism in Dystrophy, by Dr. R. Thurau, Erlangen, Germany, 32 pages

(8) Pathogenesis, Clinic and Therapy, by Dr. A. Adam, Erlangen, Germany, 92 pages

(9) Prophylaxis, by Dr. H. W. Ocklitz, Rostock, Germany, 34 pages

The American reader may be somewhat surprised about several items in the last chapter. The author stresses the importance of flies as carriers and spreaders of germs. He advocates the introduction of window screens to hinder the menace. Furthermore, he advises proper refrigeration and prophylactic typhoid-paratyphoid inoculations. All these measures, which have been used in this country in a fairly generalized fashion for about one generation, seem to have been employed haphazardly in Europe.

The quality of the paper, and with it, the clarity of the pictures, varies, at least in my copy.

ERICH STERN, M.D.

The Hazards to Men in Ships Lost at Sea, 1940-44. By R. A. McCance, C. C. Ungley, J. W. L. Crosfill, and E. M. Widdowson. Price, 5 shillings. Pp. 44, with illustrations. Her Majesty's Stationery Office, York House, Kingsway, London W. C. 2, 1956.

The shocking experience of the sinking of a great ocean liner, the Andrea Doria, in the summer of 1956 was a cruel demonstration that there may be loss of lives under circumstances where at least the environmental forces of nature are friendly to the vast majority of passengers and crew who got into life boats and were rescued promptly. This book, by McCance, Ungley, Crosfill, and Widdowson, is a sharp reminder of the several perils which beset those whose ships are destroyed in time of war where often both man and nature conspire against them. Any study such as this one made from the reports of survivors has at least some of the fallacies of the inadequacies of recollection. The sample is necessarily

biased, since only the survivors can talk. It is hardly surprising that cold and exposure bulk highest among causes of death both before and after boarding life craft. Mortality increased with time. Only 2% of those reaching life boats died if they were picked up in the second day, whereas 26% had died by the fifteenth day if rescue was delayed that long. On voyages in life craft, drinking sea water increased the death rate somewhere around tenfold. The major lessons were that better equipment was not as vital as instruction in using it, and that more realistic drills, better techniques of launching and boarding life craft, and better means of protection against the elements would have saved thousands of lives. Such information is important in an angry world.

WILLIAM B. BEAN, M.D.

Paper Electrophoresis. Edited by G. E. W. Wolstenholme and E. C. P. Millar. Price, $6.75. Pp. 232, with 74 figures. Little, Brown & Company, 34 Beacon St., Boston 6, 1956.

Interest in the techniques of paper electrophoresis has shown a phenomenal growth. From a mere handful of references in the 1940 Decennial Index and *Chemical Abstracts* the bibliography has increased to about 5000 references at the present writing. No end is in sight. Paper electrophoresis has been applied to separations of metallic ions, viral particles, and nearly everything between these limits of size and complexity. Almost as impressive as its versatility is its simplicity in practise. Even more amazing is the low cost of adequate equipment, which can be assembled by any "do-it-yourself" scientist. More sophisticated versions provide for two-dimensional separations, for continuous separations, for combinations of electrophoresis with column chromatography, and for such virtuosities as Kolin's multigradient procedures, which resolve certain mixtures in a matter of seconds. By application of isotopic labels, by specific chemical reagents, by staining with dyes, or by simple elution procedures the separated components of a mixture may be visualized and measured. The results of paper electrophoretic experiments are of significance both qualitatively and quantitatively. Such a catalogue of advantages is indeed impressive, but at the same time it constitutes a dangerous trap for the unwary. The method is too easy, and one might say that the applications have come too fast. One man's technique is as good as his neighbor's, since there is no established theoretical basis for choosing between them or for explanation of discordant results. In recognition of the situation, an international symposium was organized by the Ciba Foundation to consider possible standardization of procedures. The invited papers and accompanying informal discussions constitute the present volume. Since the participants included fervent advocates of nearly all the different instrumental approaches and at least four authors of recent extensive reviews or monographs, the discussions were far ranging and highly informative, but none of the major problems were settled.

Proper instrumentation was the subject of general discussion, but the pertinent principles were enunciated most clearly by Svennson. He demonstrated that distortion of the patterns may result from improper design of the migration chamber, and solvent distillation and paper wetness ratios may depend on the manner in which cooling is accomplished, as well as on the cooling rate. Most of the workers reported results obtained with horizontal strips, Durrum and Lederer being the only advocates of the "ridge-pole" type of equipment. The "sandwich" technique, which may introduce excessive electro-osmosis due to the different ζ-potentials of the paper strip and its supporting surface, was not often mentioned.

In free electrophoresis the migrant particles move in an essentially linear manner, disturbed only by thermal agitation. Furthermore, in free solution, migrations are conducted in what is essentially a constant environment. Not so in paper electrophoresis. Here the migration path is studded with a multitude of randomly placed obstacles, the paper fibers. As a consequence the electrical path is longer than the physical path, and the electrical path is not as nearly the same for all similarly charged particles as in free electrophoresis. A factor for correction of the potential gradient due to the presence of the paper had been previously worked out by Kunkel and Tiselius, but McDonald, who disagrees with some aspects of their theory, presented his own alternate interpretation. The significant fact is that mobility figures obtained by free electrophoresis and by paper electrophoresis are, in general, not the same. Some reported instances of identical mobilities by the two procedures may be due to a fortuitous cancellation of errors. The chief difficulty in mobility measurements on paper lies in the inconstancy of the migration environment. The presence of paper induces independent movement of the solvent with respect to movement of the solute particles, owing to the difference in charge of the paper and the solvent. Accurate measurement of apparent

movement due to electro-osmotic flow is a major problem. Certain uncharged molecules can be employed as tracers or indicators of electro-osmosis. Ideal tracers should have no charge and should follow the solvent flow perfectly. McDonald argued that the molecular volume and shape of a tracer must also be considered, a view not universally shared. As a consensus, it may be stated that precise measurements of electro-osmosis are not currently possible. Under certain conditions, electro-osmosis may be useful, serving to sharpen the migrating bands; the remarks of de Wael and Franglen dealt with this point. Laurell, Lederer, and Grassmann discussed still another disadvantage of paper as a supporting medium. Paper tends to adsorb some substances, which leads to trailing or blurring of the separated fractions. It also means that the slower moving fractions travel over an altered paper surface. Durrum indicated that at least for serum proteins neither glass nor quartz paper improved matters.

By far the greatest problem is the quantitation of the separated components. So urgent is this matter that roughly one-half of the symposium was devoted to its consideration. In the ideal case, each fraction would be separated by some distance from the others, and each would be self-identified by color or other constant demonstrable property. Each fraction could be completely removed from the strip. E. M. Crook emphasized that the separations realized in practice are far from ideal. While the eluate from cut sections may be measured in strict accordance with Beer's law, the division of a strip into sections is highly arbitrary. Several stains and numerous techniques have been advocated for the analysis of serum proteins and similar systems, but the very number of suggested procedures is a good index of the degree to which none are completely satisfactory. N. H. Martin stressed the fact that most common staining agents, including azocarmin, *Amidoschwarz*, lissamine green, etc., are quite inhomogeneous by any standard. There is little reason to expect that all the molecular species in any dye sample would have the same affinity for a given protein, or that any one species would have a constant affinity for a mixture of proteins. Successive lots of the same stain may not have the same properties. It was suggested that chromatographic purification of stains might be useful in solving this problem. In view of the the uncertainties, it was comforting to read reports showing that by very careful control of each step in the procedure several workers were able to obtain results with good precision. Franglen mentioned that seemingly innocuous parameters, like the alcohol concentration of dye baths, must be completely controlled. Repeated use of a dye bath may cause variable results as buffer salts are leached from the successive strips. McDonald reviewed his prestaining technique for serum lipoproteins, but it was pointed out by others that while without apparent effect on mobilities prestaining still is subject to many of the same errors as the more classical procedures.

In an optical sense, any stained spot on any paper strip is far from homogenous. For one thing, the dyed fractions are located on the fiber surfaces in a nonuniform way; for another, the fibers introduce considerable scattering of light. Svennson claimed that the presence of scattering imposes unique requirements on the photometric equipment. The stained strips should be "transparentized" in vacuo to obtain the highest accuracy. It was disappointing to see no discussion of reflectance photometry, which seems to offer happy prospects. McDonald argued against the common practice of dividing patterns by perpendiculars dropped through the valleys, and considerable comment was elicited by his remarks. Durrum and Sommerfelt maintained that the difference between the common practice and division by Gaussian curves was insignificant in the face of trailing errors. McDonald's position seems quite sound; there is no point in adding one error because another exists. One day the trailing problem will be solved, in which case the Gaussian division will be essential. Errors of division increase with decreasing resolution and also as the sizes of the peaks differ from one another.

Several clinical applications were described by de Wael, Köiw, Laurell, and others. Grassmann presented data on several cases of agammaglobulinemia and on a singular case of humen analbuminemia. He also showed a distinctive pattern from a case of plasmacytoma. White et al. reported interesting studies of abnormal hemoglobins, using ultraviolet absorption in the region of the Soret band to detect trace hemoglobins. Laurence and co-workers offered a detailed paper which should be required reading for anyone interested in the routine estimation of serum proteins and A/G ratios. To quote Laurence, "The electrophoretic method contains a number of variables, the more evident of which is by no means the most important." Laurell compared the patterns of proteins and of protein-bound carbohydrates in rheumatoid diseases.

Between the covers of this book is the distilled experience of many expert scientists, and while it is obviously not a book for beginners, it is impossible to overestimate its value for

those modestly familiar with paper electrophoresis. Some of the confusion has now been swept away, and it may be hoped that a sight of the bare problems will hasten effective solutions for them.

R. L. DRYER

Dictionary of Poisons. By Ibert and Eleanor Mellan. Price, $4.75. Pp. 150, with no illustrations. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1956.

In picking up a book entitled "Dictionary of Poisons" one gets a macabre feeling that he is now venturing forth into the land of the Borgias and has the uneasy sense of being an accessory before some crime done with subtle and sinister poisons. This feeling is quickly dispelled however, for after an interesting introduction, we get very sound advice about what we might do to prevent accidental poisoning, to make the home safer, the home in which some 34,000 Americans destroy themselves every year. In this destruction, poison rates as the third most common cause, and small children are the usual victims. While homicide, suicide, and accidents take the primary role, a sort of iatrogenic connivance compounded of illegible prescriptions and heroic self-overdosage by the patient may get us all in a bad fix. To this may be added the real hazard of samples coming unasked to the physician's home and often enough tested out by children when they play at being doctors or when they simply give free rein to their uninhibited curiosity.

For those who are interested in words, antimony and monks are recalled for us. Living in a state whose capital, Des Moines, literally means the monks, the word antimony has peculiar fascination. The Mellans relate part of the story about Basil Valentine, a Benedictine monk of the 15th century, who did a number of experiments with the salts of antimony. First he fed them to hogs and believed that they stimulated the growth of the hog and the tastiness of the pork. Then he tried the material out unknowingly on a number of his brother monks, some of whom are said to have died as a result of his curiosity, though this may be an exaggeration. In any event, he published his work under the charming title of "The Triumphal Chariot of Antimony" naming the material antimony, since, though it seemed to favor swine, it was against the monks in a very ominous sense.

In this book the basic attack on the problem of poisoning where prevention has failed consists of removing the poison so as to prevent or reduce its absorption into the body and then applying an antidote to counteract effects of poison already absorbed if this is possible. After each discussion, the admonition "Call a Physician" or "Call the Police for Aid" is emphasized in large print. While this book has legitimate universal appeal and might well be read by everyone, it will be particularly helpful for the doctor to have on hand when he needs to recall specific antidotes when there is little time for speculation or recollection.

In addition to its other virtues, this book may be of aid to detective story writers whose ideas of the effect of poisoning often seemed to have been derived from some ancient and lost mythology.

WILLIAM B. BEAN, M.D.

Virus Diseases and the Cardiovascular System. By Ernest Lyon, M.D. Price, $5.75. Pp. 215, with 1 illustration. Grune & Stratton, Inc., 381 Fourth Ave., New York 16; 99 Great Russell St., London, W. C. 1, 1956.

An attempt has been made to catalogue the clinical histological electrocardiographic, biochemical, and physiological changes found in the heart in viral diseases. The author points out that the more frequent use of electrocardiographic investigation and autopsy examination has lead to the appreciation of the part played by myocarditis in a subclinical form in a variety of diseases, such as mumps, polio, and influenza.

It is probably premature to publish a book on this subject, as so far only a small body of knowledge has been gathered. The book is difficult to read, as the style suggests that the text has been dictated from filing cards without any attempt to edit the presentation. The paragraphs read "Bland reported," "Elkan reported," "According to Farber and Wolbach," "Ribbert first found," etc. One must complain about the use of the words transstomachal in place of oral; "hypalbuminosis in the spinal fluid," and myocardosis. Space could have been

saved in the bibliography by having a single bibliography at the end of the book, and the space thus saved could have been constructively used by giving the titles of the articles to which reference is made.

This is a source for information on this subject for someone with a problem case.

IAN MACLEAN SMITH, M.D.

Tuberculosis in Obstetrics and Gynecology. By George Schafer, M.D., F.A.C.S., F.I.C.S. Price, $8.75. Pp. 307, with 58 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1956.

The author has pointed out how the new treatments for tuberculosis have brought many patients from sanatoria, where they were previously treated, into general hospitals, where the physicians looking after them require guidance such as is contained in this book. The text can be recommended without reservation for general practitioners, obstetricians, and gynecologists and also for phthisiologists. The author speaks from seventeen years of experience in two large tuberculosis hospitals. He gives an excellent review of the treatment of tuberculosis in general and includes good detailed bibliographies. It is interesting to note that between 1946 and 1953 the incidence of tuberculosis complicating pregnancy ranged between 1.5% and 2%. It is important to be given facts, such as "streptomycin is not toxic to the fetus."

Interesting sections included are on tuberculosis of the breast, follow-ups on tuberculous patients following pregnancy, and the fate of infants of tuberculous mothers. Dr. Schaefer is well aware of the advantages and disadvantages of BCG vaccination, and he presents the problem extremely well. Today the consensus is that therapeutic abortion because of tuberculosis is rarely indicated. In Europe and South America genital tuberculosis is found in 5% of patients attending sterility clinics, while the incidence in America is less than 1%. The author points out the importance of the involvement of the tubes in gynecological tuberculosis. The pathology of the disease is well described and is accompanied by excellent photographs and photomicrographs.

The appearance of the book and presentation of the included material is excellent. In several cases, however, statements in the text regarding investigations cannot be found in the bibliography. In summary it may be said that this is a very practical book which is lucid and easy to read.

IAN MACLEAN SMITH, M.D.

The Person Behind the Disease. By Julius Bauer, M.D. Price, not given. Pp. 136, with 5 illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York City 16, 1956.

Medical historians of the future may look back on the last seventy-five years as a period when accretions of data regarding the mechanisms of many diseases led their excited but often naïve devotees on an intellectual bender. Misunderstanding of the whole process of such disorders as infection came about largely through neglect of careful consideration of the host. This neglect, of course, was not confined just to recent times, and in the charming group of essays entitled "The Pedigree of Disease" Jonathan Hutchinson long ago emphasized the person in his striking discourse on disposition, temperament, and diathesis. In fact, these sound concepts constituted the great bulk of what our medical forefathers understood about treating the sick. It should be emphasized again and again that they treated patients wonderfully well, while we treat the disease, well enough but often to the considerable and unhappy neglect of the sick man or woman.

Julius Bauer, who has been one of the notable advocates of a study of constitution, environment, and heredity, as well as stress, strain, and injury in the cause of disease, has put together in a discursive book his views of the importance of the person behind the disease. He ranges over the problems of etiology, the uniqueness of the person, mutations, clinical syndromes, and constitutional biologic inferiority of organs and systems. In spite of its smallness, this is not an easy book to read, providing as it does a rich fare of diverse aspects of medicine, biology, and life. Much of it seems to be an assembly of eclectic observations rather than a study of a systematic development of a theme. As a reference book of the unusual it is excellent, and perhaps it should be welcomed as a small contribution to clinical lore after the manner of Hutchinson or Parkes Weber rather than that of a clinical pathfinder. And we may be grateful for such contribution, even of a rather slight kind. The appeal of the book will be to those who have matured in clinical experience rather than the beginners.

WILLIAM B. BEAN, M.D.

J. A. M. A. Queries and Minor Notes. Published for American Medical Association. Price, $5.50. Pp. 334. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1956.

To an internist it may be a surprise that the section on queries and minor notes in the *J. A. M. A.* is very popular, and there has been a continuous demand for the publication of an annual volume from which choice morsels in this section are gathered together. The book is full of fascinating tidbits, but they make very poor provender for those who are hungry for systematic facts. I find it very entertaining to read different sections of it and have contributed some notes myself. Its value as a reference book is limited by the lack of an index, even though it is arranged in logical sequence with an ample table of contents. Perhaps it may be best compared with trying to comprehend the whole of medicine by taking one of the middle books out of an encyclopedia, say FAT-FRO. The information one gets is at best partial, though what there is on the whole is quite reliable and useful. If one had at hand a complete collection of these volumes, it might be possible to get a more systematic view of the questions and particularly the answers required in certain circumstances in clinical medicine. It will appeal to the collectors of miscellaneous beads, not those who want a string of pearls. Altogether this is a rather haphazard approach to the problem of acquiring medical wisdom.

WILLIAM B. BEAN, M.D.

J. A. M. A. Clinical Abstracts of Diagnosis and Treatment. Edited by Noah D. Fabricant, M.D., Price, $5.50. Pp. 661. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1956.

This volume consists of reprints of abstracts of articles presented in the "Abstracts" section of the *Journal of the American Medical Association*. The articles are from journals published in 1955. Other than a division into sections on the various systems of the body, the classification is not rigid, although articles on one subject, such as peptic ulcer or rheumatoid arthritis, are grouped together. A vast amount of information is assembled between two covers, and the book should make good browsing for the busy doctor who has not a great deal of time for reading.

W. L. BLOOMFIELD

Preventive Medicine in World War II. Vol. III. Personal Health Measures and Immunization. Office of Surgeon General, Department of the Army. Price, $3.25 (Buckram). Pp. 394, with illustrations. U. S. Government Printing Office, Washington 25, D.C., 1955.

Some of us thought we were lucky to be in the Medical Corps during World War II. Many others thought they were unfortunate. A few were downright paranoid about it. Those not in uniform fell into the same groups but not in the same proportions. Some guilt feelings were manifest. A few of us will recall a time when enthusiasm had not been dampened by the blasé attitude which settles over us with the tightening of joints, the hardening of lenses, and the sclerosis of ideas. It was a period whose saving grace for young physicians in the Armed Forces was a byproduct of modern research in clinical medicine, applied physiology, environmental and preventive medicine, as well as the more spectacular fields of surgery. Here, for the first time, with inspiration born of urgency, the main body of clinical research in America and elsewhere was turned to a comprehensive exploration of the soldier—"normal man"—of his ability to adjust to surrounding changes, and of the harm produced by physical agents when adequate adjustments were not possible. Many disciplines rarely considered pertinent to medicine were directed toward the immediate solution of the difficulties encountered by the soldier as modified by his tank, plane, craft, vehicle, or his own personal locomotion, not to mention those of his enemy.

This book manages to give in outline and often in detail some of the aspects of preventive medicine seen through the eyes of the senior officers who have contributed to this volume in the series dealing with the medical history of the Army in World War II. Perhaps because this historical enterprise has not been the responsibility of any single person, and the part-time contributors have only one eye on the subject, the character of this book is disappointing, both as a history and as a reference book. Our ideas about wars and, in fact, our ideas about military medicine might be radically different if the writing of the history had been in the hands of the lieutenants and captains who, being at the center of things, did the actual deeds.

They should tell the story rather than those whose direction was essential but whose intimate contact with affairs was in the higher levels of policy dealing with strategic matters rather than with the tactics of everyday life in war or peace.

Not only was there great excitement, but there was much progress in our understanding of man—normal man who bounced about buffeted by all sort of physical forces including his own physiologic and emotional reactions to fear, anxiety, noise, bodily injury, and often enough sheer ennui. What a pity the exciting and momentous works described here could not have been embodied in a less pedestrian chronicle. Thus what might have been a magnificent and inspirational volume has, I think, lost the essential flavor of the time. Perhaps this is inevitable of anything written in a period when man seems bent on destroying himself and when the folly of nations follows unerringly the devious but sure lines of perverseness. This book will be a useful reference for those interested in medical history, but for those who made this history, their own views, actions, and philosophy may be hard to recognize.

WILLIAM B. BEAN, M.D.

News and Comment

ANNOUNCEMENTS

Sixth International Meeting of Geographical Pathology.—The Sixth International Meeting of Geographical Pathology will be held in Paris on July 9, 10, and 11, 1957, in the Grand Amphithéâtre de l'Ancienne Faculté de Médecine, 12 rue de l'École de Médecine, Paris 6ème, with Prof. Jacques Delarue as Chairman.

The theme of the meeting will be the geographical pathology of gastroduodenal ulcers. Details of the program will be announced shortly. For complete information, address the General Assistant Secretary of the National Committee of France: Dr. J. P. Hardouin, 21, avenue Pierre ler de Serbie, Paris 16éme.

Research Fellowship Awards.—The Public Health Service has announced 44 five-year research fellowship awards to scientists in 29 universities and medical schools in 20 states, the District of Columbia, and Canada.

The awards are the first in a new Federal program designed to increase manpower for research in the basic medical sciences.

Recipients are scientists who have completed their doctor's degrees in biochemistry, pharmacology, physiology, microbiology, pathology, and the psychological sciences.

Each fellow will receive a salary not to exceed $10,000 yearly, plus up to $2000 to defray part of the expenses of his research. The salary level is set by the institution to approximate the salaries of scientists doing similar research and teaching as members of the regular faculty.

These fellowships will permit recipients to continue their research activities. Concurrently, the sponsoring institutions will assign appropriate teaching responsibilities so that fellows may qualify for full-time academic positions at higher levels.

Dr. Leroy E. Burney, Surgeon General of the Public Health Service, said the program is designed to meet a shortage in the early career opportunities by which medical scientists may be trained for combined research and teaching posts.

The new program results from over two years of study by the Public Health Service, aided by a panel of outside experts and the advice of deans of medical schools and heads of university departments concerned with research and teaching in the basic medical sciences.

In citing the need for the senior fellowships, the Surgeon General said a recent survey revealed that for the current year over 200 authorized and budgeted positions on the faculties of medical and basic science schools are unfilled. Included are 55 professorships, 52 associate professorships, and 79 assistant professorships. He added that approximately the same number of vacancies existed last year.

The P. H. S. will award between 40 and 50 new fellowships annually until approximately 250 have been given by the fifth year. Thereafter the program will be maintained at this level until the national deficiencies have been met. The total cost of the first year of the program will be in the neighborhood of $500,000.

Meeting of American Trudeau Society.—The 52nd Annual Meeting of the American Trudeau Society, medical section of the National Tuberculosis Association, will be held in Kansas City, Mo., May 6 to 9, 1957, in conjunction with the Annual Meeting of the National Tuberculosis Association.

In addition to scientific sessions at which papers will be presented on current research, plans are being made for seven special lectures and four panel discussions. Topics for the latter will be tuberculin testing, fungous diseases, tuberculosis case finding, and the surgical approach to the bad chronic case of tuberculosis.

The lectures will be on cor pulmonale, chest injuries, hazards of radiation, tuberculosis in animals, histologic studies in smoking, mucovisidosis, and diseases of the diaphragm.

Clinical Investigator Program.—The Veterans Administration announces a clinical investigator program.

Purpose

The needs of the Veterans Administration Medical Program and the potential of its research and education activities in contributing to the health of the nation are such that it is planned to train selected physicians and dentists whose primary responsibility will be medical research. The candidates for this appointment must be interested in problems of particular importance in the care of veteran patients in fields basic to neurology and psychiatry, cardiovascular disease, cancer, degenerative diseases, and problems involving the aging process. Maximum freedom of choice of subject will be allowed within these broad fields.

Eligibility

Any physician or dentist who has completed at least the formal residency training period required prior to American Specialty Board certification and because of special interest and aptitude wishes to do full-time research for a period of possibly up to three years is eligible.

General Plan

The clinical investigator will spend at least three-fourths of his time in research. The balance of his time may be spent in teaching and patient care or in whatever professional activity he and his sponsors agree is advantageous for his development. He will be appointed as a full-time member of the Veterans Administration hospital staff, and his official title will be Veterans Administration Clinical Investigator. He will be entitled to the privileges and benefits of other full-time physicians and dentists, such as insurance and retirement eligibility and annual and sick leave. All clinical investigators will have research as their primary responsibility; they will, in addition, hold suitable clinical appointments on the hospital staff which will enable them to enjoy the privileges of a responsible relationship to the patient care program.

Salary

The clinical investigator will be appointed at intermediate grade. The beginning salary is $8990 per annum. Additional credit will be given for American Specialty Board certification in accordance with existing regulations.

Nomination and Selection

Candidates are nominated to the Veterans Administration hospital manager through the Veterans Administration Hospital Research Committee for approval by the Deans Committee. From the group of nominees the clinical investigators will be selected by the Central Advisory Committee, composed of outstanding educators and investigators.

Form of Application

The candidate should submit a *curriculum vitae,* including transcripts of his scholastic record and any other information which might help the committee in its evaluation. He should prepare a detailed description of his proposed research program and make a brief statement of his future plans and ambitions. The candidate should select a preceptor who will follow his career throughout the period of appointment. The preceptor may be any person approved by the Deans Committee, within or without the Veterans Administration. The sponsoring hospital will describe the research and other facilities available for use by the investigator. Additional information and assistance in completing the application should be secured from the Deans Committee or hospital manager. In making the final selection the Central Advisory Committee will consider not only the qualifications of the candidate, but the ability of the hospital to provide an atmosphere conducive to his development.

Time of Awards

Selection will be made semiannually for January and July appointment. Applications may be obtained from the manager of the Veterans Administration hospital of choice. The completed forms are submitted by the Deans Committee to the Office of the Assistant Chief Medical Director for Research and Education, Veterans Administration, Washington 25, D. C. The candidates will be notified of their selection by the Chief Medical Director through the hospital manager and an announcement of the appointment will be made to the Deans Committee at the same time.

Seventh International Cancer Congress.—The Seventh International Cancer Congress will be held in London, England, July 6-12, 1958, under the Presidency of Sir Stanford Cade. Congress headquarters will be The Royal Festival Hall.

There will be two main sessions of the Congress: (*a*) Experimental and (*b*) Clinical and Cancer Control.

Special emphasis will be placed on hormones and cancer, chemotherapy, carcinogenesis, and cancer of the lung.

Proferred papers will only be considered if submitted with an accompanying abstract (not over 200 words) before October, 1957, and if dealing with new and unpublished work.

The registration fee for the Congress will be £ 10 or $30 and the latest date for registration without late fee will be Jan. 1, 1958.

Registration forms and a preliminary program will be available early in 1957 on application to The Secretary General, Seventh International Cancer Congress, 45 Lincoln's Inn Fields, London, W. C. 2, England; J. H. Maisin, President, Union Internationale Contre Le Cancer, Voer des Capucins, 61, Louvain, Belgium, or Harold Dorn, Secretary General, Union Internationale Contre Le Cancer, National Institute of Health, Bethesda 14, Md., U. S. A.

Fellowship in Hematology.—A one-year appointment (option of renewal) beginning July 1, 1957, is available in the Department of Medicine, University of Maryland School of Medicine. Annual stipend $3000-3500 (dependent on marital status). The fellowship offers opportunities for training in clinical hematology as well as investigative work in this field. Inquiries should be addressed to Dr. Milton S. Sacks, Professor of Clinical Medicine, University Hospital, Baltimore 1.

PERSONAL

Appointment to the National Advisory Heart Council of Dr. Howard P. Lewis, professor of medicine, University of Oregon Medical School, Portland, Oregon, has been announced by the Surgeon General, Leroy E. Burney, of the Public Health Service, U. S. Department of Health, Education, and Welfare.

Dr. Lewis, who is also chief of medicine at the University hospitals, has been with the school since completing his residency. He is an honorary staff member of Good Samaritan and Providence hospitals in Portland. Dr. Lewis served as a colonel with the Army Medical Corps during World War II; was chief of medical service at Rhoads General Hospital, and Consultant in Medicine to the Second Service Command.

A native of San Francisco, Dr. Lewis is a member of the Pacific Inter-urban Clinical Club, the American Heart Association, American Medical Association, the North Pacific Society of Internal Medicine, the Society of Medical Consultants of the Armed Forces, the American Federation of Clinical Research, the Western Society for Clinical Research, and the American Clinical and Climatological Association. He is a Regent and former Vice President of the American College of Physicians and Member of Examining Board, American Board of Internal Medicine.

He is the editor of the monthly, *Modern Concepts of Cardiovascular Disease*, published by the American Heart Association.

As a member of the National Advisory Heart Council, he will make recommendations to the Surgeon General on programs of the National Heart Institute, established by Congress through the National Heart Act in 1948. This is one of the seven National Institutes of Health at Bethesda, Md., main research arm of the Public Health Service.

A 15-member group composed of outstanding leaders in medicine, science, education, and public affairs, the Council was also established by the National Heart Act as official advisory body for the National Heart Institute. The Council reviews requests from nonfederal institutions and individual persons for research and teaching grants in the field of diseases of the heart and circulation. The group is the recommending authority for these grants which are awarded, from funds appropriated by Congress, by the Surgeon General after they have been recommended by the Council for approval.

In addition to appointed members of the National Advisory Heart Council there are three exofficio members representing the Public Health Service, Veterans Administration, and Department of Defense. The Council meets three times a year at the National Institutes of Health in Bethesda, Md.

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* Smith, J. A.: *J.A.M.A.*, 152:384, May 30, 1953. Brown, W. T., and Smith, J. A.: *South. Med. Jour.*, 46:582, June, 1953. Smith, J. A.: *Postgrad. Med.*, 16:316, Oct., 1954. McCullagh, W. H.: *Jour. Florida Med. Assn.*, 41:718, Mar., 1955.

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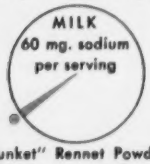

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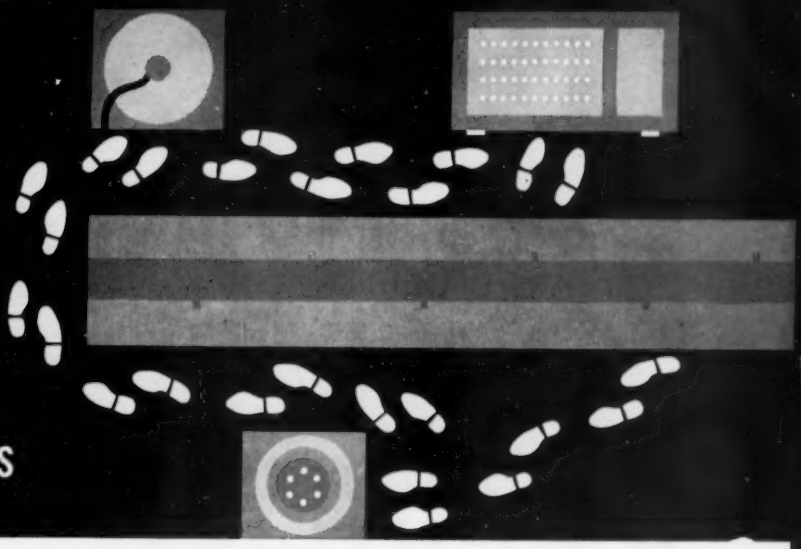

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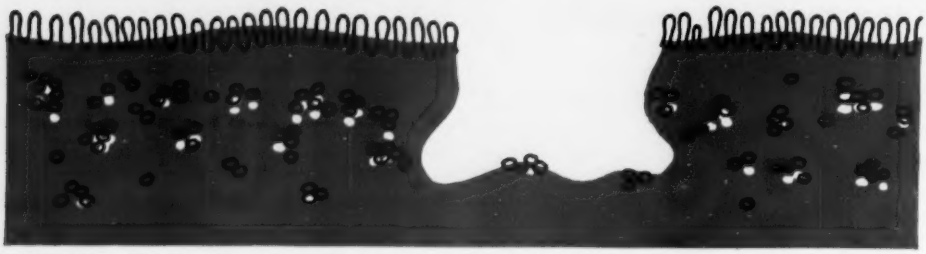

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Sokoloff, O. J.: A.M.A. Arch. Dermat. 74: *393, 1956.*

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Thimann, J. and Gauthier, J.W.: Quart. J. Stud. Alcohol. 17: *19, 1956.*

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Borrus, J.C.: J.A.M.A. 157: *1596, 1955.*

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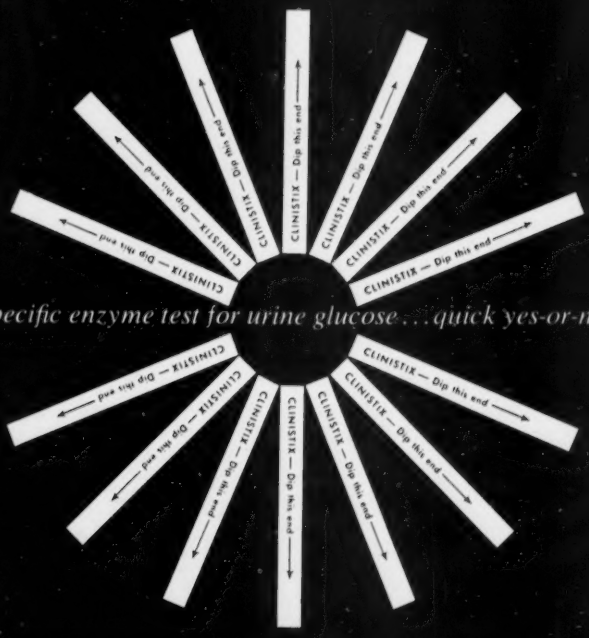

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1. Knoch, H.R., and Kirk, R.: Proclorperazine—A New Agent for the Treatment of Psychic Stress, in manuscript.

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